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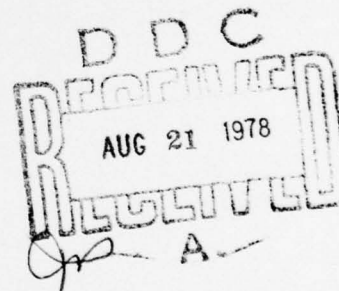
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ANNUAL RESEARCH PROGRESS REPORT

U.S. ARMY INSTITUTE OF SURGICAL RESEARCH  
BROOKE ARMY MEDICAL CENTER  
FORT SAM HOUSTON, TEXAS 78234

1 October 1976 - 30 September 1977

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Prepared for:  
US ARMY MEDICAL RESEARCH & DEVELOPMENT COMMAND  
WASHINGTON, D.C. 20314

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) This report documents the clinical and laboratory activities of the US Army Institute of Surgical Research during the fiscal year 1977. These activities include patient care, clinical investigation and laboratory research in the areas of (1) burn injury, (2) acute renal failure, and (3) general trauma. Special emphasis is placed on the clinical management of burned patients and on studies related to prevention and treatment of burned wound infection.		

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1. The first part of the document is a letter from the President of the United States to the Congress, dated January 1, 1861. It is a formal address, and it is the first of its kind since the signing of the Constitution. The President, James Buchanan, is addressing the Congress, and he is doing so in a very formal and dignified manner. He is discussing the state of the Union, and he is discussing the issues that are facing the country at that time. He is also discussing the role of the President, and he is discussing the responsibilities of the Congress. The letter is a very important document, and it is a very interesting one to read. It gives us a glimpse into the mind of a President, and it gives us a glimpse into the state of the country at that time. It is a document that is worth reading, and it is a document that is worth studying.

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DEPARTMENT OF THE ARMY  
US ARMY INSTITUTE OF SURGICAL RESEARCH  
BROOKE ARMY MEDICAL CENTER  
FORT SAM HOUSTON, TEXAS 78234

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BASIL A. PRUITT, JR., M.D.  
Colonel, MC  
Commander & Director

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## FOREWORD

The clinical care and research reported herein are not only mutually dependent but mutually amplifying. The burn patient is a model of all injured men and as such the information generated in the course of our care and research can and has been applied to improve the care of all injured soldiers--the ultimate beneficiaries of this work.

This Institute, which celebrated its Thirtieth Anniversary this year, has served as the model for many of the burn centers which have been established elsewhere during the past three decades. The synthesis of clinical care and research into a unified whole has maintained the relevance and enhanced the effectiveness of our investigative activities. Although perhaps unique within the military, this integration of clinical and laboratory capabilities is precisely that in effect in all academic institutions and burn centers today. The Institute's problem solving research has been carried out by an effective alloy of a multidisciplinary clinical and research staff to advance the care of injured man in the fields of fluid resuscitation, inhalation injury, infection and host resistance, stress ulcers and metabolic support. The many achievements of this institute, the work detailed in this volume, and the regard in which the Institute is held in the national and international medical community underlines the surgical corollary of the aphorism, "The proper study of mankind is man", i.e., the proper study of injured man is the burn patient.

*Basil A. Pruitt, Jr.*

BASIL A. PRUITT, JR., MD, FACS  
Colonel, MC  
Commander & Director



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<p>23. (U) The Clinical Division of the US Army Institute of Surgical Research continues its role as a major specialized clinical treatment center for thermally injured military personnel. Its main objectives are the investigation and modification of new diagnostic and therapeutic methods for optimum care of the burn patient as well as dissemination of the scientific advances to military and civilian medical treatment centers.</p> <p>24. (U) Thermally injured patients both from the Continental United States and throughout the world are evacuated to the US Army Institute of Surgical Research for intensive inpatient therapy. Carefully controlled evaluation of the efficacy of many treatment modalities is undertaken.</p> <p>25. (U) 76 10 - 77 09 During 1976 the number of patients admitted to the Institute of Surgical Research increased to 257. General principles utilized in the management of burned troops remained basically unchanged. Early burn problems receiving special attention included initial resuscitation and inhalation injuries. Further studies with more sophisticated cardiovascular monitoring have indicated that the addition of cold early in the resuscitation may significantly improve the hemodynamic status of burn respiratory supportive care including expanded use of assisted mechanical ventilation has taken place. It was determined that the prophylactic administration of nebulized gentamycin in patients with inhalation injury did not improve survival. The use of new topical therapeutic agents and other methods of wound care are undergoing clinical evaluation. Continued extensive use of the operative facility is apparent with a total of 1,269 operative procedures and the administration of 427 general anesthetics.</p>							

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ANNUAL PROGRESS REPORT

PROJECT NO. 3S1611102BS05-00; MILITARY BURN RESEARCH

REPORT TITLE: CLINICAL OPERATION, CENTER FOR TREATMENT OF BURNED SOLDIERS

US ARMY INSTITUTE OF SURGICAL RESEARCH  
BROOKE ARMY MEDICAL CENTER  
FORT SAM HOUSTON, TEXAS 78234

1 January 1976 - 31 December 1976

Investigators:

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ABSTRACT

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US Army Institute of Surgical Research, Brooke Army Medical Center, Fort Sam Houston, Texas 78234

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In the year 1976 there were 257 patients admitted to the Clinical Division of the United States Army Institute of Surgical Research for treatment of thermal injuries. The main emphasis of the Institute continues to be provision of optimal medical care to military personnel and authorized civilians with major thermal injuries. Original scientific clinical investigation has been maintained at a high level with research into the pathophysiologic, biochemical, metabolic and bacteriologic aspects of thermal injury. Several newer clinical approaches utilizing diagnostic and therapeutic advances are being applied in the treatment of extensive thermal injuries. Major areas of research include initial hemodynamic response to thermal injury and alteration of cardiovascular

dynamics with different modes of resuscitation, alterations in pulmonary function and pulmonary complications in burn victims, continued studies in metabolism and nutritional problems associated with burns, secondary alteration of host resistance and its effects on the development of infection and sepsis, studies of acute renal insufficiency and renal functional changes, pathophysiologic gastrointestinal alterations and their prevention and the evaluation of the burn wound care and environmental alteration for improved patient survival. This report summarizes the activity of the Clinical Division of the United States Army Institute of Surgical Research in 1976 and cites the types of treatment, response to treatment, and recognizable complications which have contributed to morbidity and mortality in the burn patients.

Topical therapy  
Sulfamylon  
Wound excision  
5% Sulfamylon acetate  
Humans  
Autografts

## CLINICAL OPERATION, CENTER FOR TREATMENT OF BURNED SOLDIERS

The Clinical Division of the United States Army Institute of Surgical Research continued through the year 1976 to provide the clinical care required for the treatment of thermally injured soldiers and other authorized patients. The Division also carries out clinical research to identify and evaluate new and improved techniques of patient management and burn treatment.

The number of burn patients admitted increased from 245 in 1975 to 257 in 1976 with the latter including 213 males and 44 females. Burn patient age ranged from 6 months to 86 years. The average extent of burn was 38.3% of the total body surface and the average burn index was 26.5.

During calendar year 1976 a total of 77 aeromedical evacuation flights were carried out to effect the transfer of 103 patients to the Institute. Seventy-five of these flights were carried out within the Continental United States to transfer 100 patients to the Institute. All patients within a radius of 200 miles of Brooke Army Medical Center requiring air evacuation were transported by a United States Army MAST helicopter unit with nine such flights made during the year to transport burn patients. Forty per cent of all admissions to the Institute during the referenced year were transported by aeromedical evacuation means with 12% of these being transported by helicopter.

### CLINICAL MANAGEMENT

The principles of resuscitation of thermally injured patients remain constant but some evolution of resuscitation techniques has occurred over the past decade. Prompt and adequate fluid resuscitation of all burn patients and maintenance of an adequate airway in burn patients with concomitant inhalation injury continue to have the highest priority in initial concomitant inhalation injury continue to have the highest priority in initial care. Following admission and after initial evaluation and stabilization continued observation and clinical monitoring is necessary to detect the need for escharotomy, the presence of initially inapparent inhalation injury and in patients with high voltage electric injury, the need for early surgical exploration. On the completion of resuscitation the burn wound assumes priority of care and during the past year early surgical excision has been more frequently employed. Nutritional management and support has increased both in intensity and sophistication during the past year, with improved feeding regimens by both the enteral and parenteral routes directed towards minimizing weight loss, maintaining body mass and providing diets containing all essential nutrients. Clinical studies conducted in the course of patient care have increased the understanding of post injury pathophysiology and have provided clinical insight leading to alteration and improvement in the care of the burn patient.

Fluid resuscitation: During 1976 initial fluid management for the extensively burned patient consisted principally of the administration of lactated Ringer's solution with adequate resuscitation achieved in the majority of patients. It was noted however that patients with extensive burns frequently received greater volumes than would be estimated by the formula for predicting fluid needs. These latter patients requiring greater resuscitation volumes appeared to have a higher complication rate with a more prolonged period of post injury ileus and a greater incidence of fluid overload as manifested by congested heart failure following resuscitation. It was further noted that the administration of colloid containing fluids to those patients unresponsive to the usual resuscitation volumes would improve their cardiac output and increase their left ventricular end diastolic volume. These findings have prompted renewed study to define more accurately the optimum composition of resuscitation fluids. The clinical evaluation of the effect of resuscitation fluids on pulmonary and systemic hemodynamic indices also provides physiologic monitoring data of direct usefulness in the management of the individual patient who responds to resuscitation in other than the anticipated manner.

Diagnosis and Treatment of Inhalation Injury: The incidence of concomitant inhalation injury in our burn patient population remains high. This high occurrence rate reflects both an improved accuracy and sensitivity of diagnosis and improved initial care permitting the transfer and admission of more seriously burned patients to the Institute. Greater attention has been given to initial evaluation of the airway for the identification of inhalation injury. Although the administration of sympathomimetic amines by nebulization appears to limit airway edema in a select group of patients, earlier endotracheal intubation is carried out in the majority of patients with inhalation injury. Intubation insures airway patency in patients with severe inflammatory change in the upper airway and incipient airway obstruction. Careful evaluation of the airway status in each burn patient by the physician member of the air evacuation team is carried out with endotracheal intubation to facilitate patient management during aeromedical transfer performed in those patients with evidence of airway obstruction. In association with more frequent intubation mechanical ventilatory support has also been more frequently used. The use of intermittent mandatory ventilation during the current year has reduced the adverse physiologic effects which occur with tracheal intubation in the absence of mechanical ventilation. The intermittent insufflation of large tidal volumes minimizes the predisposition to atelectasis in intubated burn patients resulting from their loss of the ability to cough and the reduced tidal volume characteristic of post burn tachypnea.

The <sup>133</sup>Xenon lung scan and direct examination of the tracheobronchial tree using the fiberoptic bronchoscope continued to be the two diagnostic modalities most frequently used to identify the presence of inhalation injury. All burn patients suspected of having inhalation injury undergo fiberoptic bronchoscopy as part of their admission studies. The examin-



ation is done by the transnasal route utilizing topical anesthesia with intubation carried out when significant upper airway swelling is identified. The presence of tracheobronchial mucosal damage is considered diagnostic of inhalation injury with probable involvement of the lung parenchyma. A  $^{133}\text{Xenon}$  ventilation perfusion lung scan is performed on all patients suspected of having an inhalation injury who can be transported to the Nuclear Medicine Clinic where the test is performed. The  $^{133}\text{Xenon}$  lung scan is usually omitted however in those patients with obvious inhalation injury by bronchoscopic examination. The interpretation of the lung scans is also influenced by the fact that falsely positive examinations can be obtained in patients with chronic lung disease and those with acute respiratory infections existing at the time of burn injury. Patients in whom the diagnosis of inhalation injury is made are begun on a specific treatment protocol with a graduated therapeutic response keyed to the severity of respiratory impairment. Clinical monitoring of such patients includes scheduled periodic assessment of pulmonary function, measurement of arterial blood gases and serial evaluation of chest roentgenograms. Additional treatment modalities include the administration of humidified oxygen, elevation of the upper trunk and head, and the use of incentive spirometry, IPPB, bronchodilators, chest percussion and postural drainage, to minimize the sequelae (atelectasis, shunting, and pneumonia) which commonly result from inhalation injury. Recent clinical studies have shown that systemically administered steroids, parenteral antibiotics and administration of nebulized antibiotics as prophylactic measures have no discernable effect on the outcome of inhalation injury in burn patients.

Topical Therapy: In 1976 silver sulfadiazine continued as the initial primary topical chemotherapeutic agent. The early success that was noted to have diminished in 1975 showed further diminution throughout the reporting period of 1976. Klebsiella became the predominant organism responsible for burn patient sepsis late in 1975 and remained the most common invasive organism in early 1976. Later in the year an increase in the incidence of Pseudomonas infections secondary to burn wound invasion was noted. A pattern of generalized increase in the resistance of gram negative organisms to silver sulfadiazine seemed to be paralleled by early positive blood cultures and a more rapidly deteriorating clinical course with sepsis leading to death in these patients. As gram negative infection was again the most common cause of death in the patients in our unit a new plan of therapy utilizing both silver sulfadiazine and Sulfamylon was instituted. In patients with either clinical signs of invasive burn wound infection or burn wound biopsy with histologic confirmation of invasive burn wound infection, the use of the topical antimicrobial agents in alternate application was undertaken.

Following the daily wound cleansing, the wounds were placed in Sulfamylon burn cream and the patient closely monitored for the development of signs of either pulmonary or metabolic deterioration.

The patient's wounds were cleansed again 12 hours later and silver sulfadiazine was then applied and left in place overnight. In addition to the alternate use of the topical antimicrobial agents, areas of burn wound infection received twice daily subeschar injections of carbenicillin. Utilizing this regimen the high incidence of pulmonary complications as seen in previous years with the continuous application of Sulfamylon burn cream was not encountered. The occasional patient who developed tachypnea and pulmonary infiltrates uniformly improved when placed back in continuous silver sulfadiazine topical therapy and treated with diuretics. In patients in whom it was necessary to continue the use of Sulfamylon burn cream because of extensive wound sepsis due to a gram negative organism, a nasotracheal tube was placed and ventilation mechanically assisted. Although their pulmonary condition usually improved with such treatment most of these patients ultimately succumbed with sepsis. Improved survival in the 15-40 year age group would seem to confirm some effectiveness of this regimen of wound care. Careful monitoring of the pulmonary status of patients placed in Sulfamylon is mandatory because of the accentuation of post burn hyperventilation associated with this topical antimicrobial agent.

Burn Wound Excision: The usefulness of burn wound excision was further evaluated in 1976. Excision of the burn wound and subcutaneous tissue down to the level of the investing fascia, excision of eschar to viable subcutaneous fat and tangential excision with removal of the necrotic tissue of second degree burn wounds were all utilized. As previously noted excision to the level of the fascia as treatment for extensive burn wounds was comparable to nonsurgical treatment. However, such excision in patients with moderate sized burns (40-60% total body surface area) resulted in improved survival. Nearly 100% autograft acceptance was commonly noted in such patients undergoing excision to the level of the investing fascia in whom immediate autografting was carried out. Negative nitrogen balance, the development of infection or the appearance of other significant complications did impair graft adherence in some patients. An alternate approach to the application of autograft on fascia was the use of fresh allograft. Excellent results with the rapid appearance of granulation tissue and subsequent complete acceptance of autografts was the rule. Other methods of wound coverage in patients undergoing that form of excision were associated with a high incidence of wound degeneration and wound infection.

Excision of the eschar to viable tissue was advantageous in selected patients. In our experience the acceptance of immediately applied autografts on such wounds has been unsatisfactory. Therefore, such wounds are either dressed with gauze soaked in 5% Sulfamylon solution or covered with biologic dressings. Following the development of granulation tissue autografting can usually be undertaken between seven and ten days following excision. In patients with donor sites insufficient for total coverage at the time of initial autografting, areas of open wound can be maintained in allograft on an interim basis.

Tangential excision was exclusively used in the treatment of deep second degree burns of the dorsum of the hand. Such excisions are performed when the patient is stable following initial resuscitation. Patients who are not candidates for general anesthetic either because of the presence of an inhalation injury or for other reasons may have the operative procedure performed under regional anesthesia if a satisfactory unburned access route is present. We prefer the use of the guarded Blair knife over the dermabrader since it will cause less trauma to the remaining wound bed in the zone of stasis. The dermabrader is utilized in focal areas where the Blair knife cannot be employed to remove the burned tissue. Thrombin soaked gauze sponges are applied to promote hemostasis and following this autograft skin meshed 1:1 1/2 is applied without expansion. Uniformly excellent graft acceptance was the rule which allowed earlier motion with rapid resolution of hand edema and marked improvement in long term function.

Nutrition: Metabolic studies relating nutritional status of patients to wound healing and other body organ system function have resulted in increased emphasis on appropriate caloric intake in patients. Currently the administration of calorie and nitrogen containing compounds is started on the third or fourth post burn day. At this time half-strength hyperalimentation fluid in a 10% dextrose medium is administered as the intravenous maintenance fluid. This 3 1/2% amino acid solution has the advantage of ease of administration through a peripheral vein, fewer adverse metabolic responses with change in rate of infusion, and a lower potential for solution growth of microbial organisms. The aim of this intravenous preparation is twofold; to increase the caloric intake of patients as soon as possible, and to decrease the amount of protein catabolism which occurs following thermal injury. Once the initial gastrointestinal ileus has abated, high calorie high nitrogen oral feedings are encouraged. In addition all patients receive nutritional supplements which are meant to augment both the caloric and nitrogen intake. In this manner calorie and nitrogen balance can be approximated. In patients who either cannot or are unwilling to eat but still have gastrointestinal tract function, a feeding tube is passed with the continuous administration of tube feeding or bulk free chemically defined diets. Low volume continuous administration of hypertonic nutrient solutions with gradual increase in the volume and tonicity of the administered tube feeding has resulted in satisfactory caloric balance without significant diarrhea in most patients.

In those patients who cannot receive adequate nutritional support via the gastrointestinal tract, parenteral hyperalimentation is used. Intravenous hyperalimentation may be instituted as early as four or five days following a burn injury and follows standard methods well described in the medical literature. Unburned anatomical sites should be preferentially utilized for insertion of the central venous line necessary for hyperalimentation. However, insertion of a central venous cannula through burn wound is readily undertaken if no burn-free site is available. Meticulous asepsis during central venous line insertion,



application of an antimicrobial ointment at the catheter insertion site, ultra-filtration of the infusate, avoidance of additional piggyback infusions into the hyperalimentation system and frequent changes of the central infusion lines have been standard practice and have resulted in a low incidence of infusion related septic complications. The use of intravenous fat emulsion solutions to supplement caloric intake was increased in 1976. Twice weekly administration of 500 or 1,000 ml of intravenous fat emulsion were utilized in patients receiving parenteral hyperalimentation. The devastating metabolic effects of generalized sepsis emphasize the need for insuring the administration of supranormal calorie intake to these patients. Oral or parenteral alimentation was utilized as indicated to accomplish this goal.

Research: The Institute of Surgical Research clinical staff also conducts research and during 1976 initiated several such investigational projects. Current research projects include renal studies, hemodynamic studies, studies of infection and sepsis, gastrointestinal studies, host resistance studies, metabolic studies, pulmonary studies, and studies of the various methods of wound care. These clinical studies into a wide variety of aspects of post injury pathophysiology have provided increased knowledge and understanding resulting in therapeutic advances in the treatment of burn injuries and other injured patients. This information has been widely disseminated through presentations at professional meetings of national and international scope and by publication in referenced medical journals. Research projects are reviewed in depth in other sections of this report.

Education: Educational activities, another major function of the Institute involve staff physicians, nursing service personnel, and members of all other branches of the Clinical Division. Bedside and didactic instruction of physicians of varying experience and training levels spending a variable time at the Institute is emphasized to enhance their capability in the management of burn injuries. Between one and four resident surgeons from various military and nonmilitary training programs are present at the Institute at any given time for such experience. Multiple lectures are given by our physicians each year at the Academy of Health Sciences, for the Intensive Nurse Clinician Courses, and for groups of interns rotating through the Emergency Room at Brooke Army Medical Center. Other military teaching commitments include formal rounds with the general surgery resident staff and faculty at the Brooke Army Medical Center twice monthly and a teaching conference at least once a month. Multiple presentations as requested by other military installations throughout the United States are given each year. Procedural information and treatment protocols concerning burn care for formal manuals and isolated teaching documents utilized by all branches of the armed services are provided as requested. The Institute itself conducts both a research conference and grand rounds on a weekly basis. In addition to these responsibilities, members of the Institute of Surgical Research are frequently called on to present lectures as part

of teaching seminars on burn care and the Institute at times supplies the entire faculty to present such seminars. Scientific presentations of original research findings are presented at many national scientific forums. In addition requests for less formal discussions concerning the treatment of burns and burn prevention from many community service groups are honored each year as time and workload permit. These teaching efforts of Institute members have resulted in improved burn care personnel capabilities and improved care of burn patients.

#### MORBIDITY AND MORTALITY

Seventy-nine of the 260 patients for whom disposition was made during calendar year 1976 expired in the hospital for an overall mortality of 30.4%. Of the patients expiring 56 were male and 23 were female. The average extent of burn for the nonsurviving patients was 64.2% of the total body surface with there being 31.1% average third degree burn. The average burn index of this group was 47.7. Autopsies were performed on 53 patients or 67% of all deaths. Five patients (0.52% expired during acute resuscitation on the day of burn. On the average, death occurred on the 12th post burn day.

Only four patients in the nonsurviving group were under 15 years of age or 5% of the fatalities. In the pediatric age group the average total burn size for nonsurvivors was 73% total body surface burn with an average of 46% third degree burn. The average burn index was 59.5. All patients who died had third degree burns and three of these patients had post mortem examination.

Sepsis was the most common cause of death in 1976. Fifty one deaths were attributed to sepsis. Klebsiella was the most common organism responsible for the septic deaths with 57% of such deaths attributed to this organism. Pseudomonas organisms accounted for only 25% of all mortality and Staphylococcal organisms were implicated as causing 16% of the deaths. A single case of death due to Entamoeba histolytica infection was recorded. Severe inhalation injuries with acute respiratory failure and superimposed pneumonia accounted for 22% of all deaths and all other causes combined were responsible for 16% of the deaths. Table 7 lists the specific cause of death for patients in 1976.

#### COMPLICATIONS

Infection was the most common complication noted. There were 285 recorded infections in 1976 or 1.1 infections per patient during their hospitalization. Of these infections 243 were caused by bacteria, 40 were caused by fungi and two were caused by viruses. The most common infection in the unit was septicemia occurring in 111 patients (42% of admissions). In these patients the burn wound was established as the source in 63 (24% of admissions). As previously stated 51 or 46% of patients with sepsis died. The majority (29 or 57%) of these deaths were due to Klebsiella organisms. Pseudomonas sepsis accounted for 13

deaths or 25% of the septic deaths. Only eight deaths were attributed to staphylococcal sepsis (16%) and these infections were predominantly felt to be secondary to septic thrombophlebitis. One case of *Entamoeba histolytica* sepsis causing death was recorded. A total of 2,696 blood cultures were drawn during the year 1976. This represents an average of 7.3 blood cultures drawn per day and a total of 15% of the drawn blood cultures were positive for microbes. Other complications will be discussed by anatomical location.

During 1976, 77% of all admissions had some type of head, face or neck burns. This injury was associated with a significant number of complications. Thirty-nine patients or 15% of admissions had some type of ear complication. Otitis media was the most common complication and occurred in 26 patients with a total of 43 ears being affected. Twenty-two patients (35 ears) had to have operative incision, drainage, and chondrectomy of the ears. The majority of these infections continue to be caused by gram negative organisms. The incidence in recent years has not changed even with the continuous application of Sulfamylon to burned ears. A variety of eye injuries and complications occurred. There were eight corneal burns, one corneal laceration and eight corneal abrasions noted on admission. In patients with these injuries four developed corneal ulcers, three developed conjunctivitis and in one patient an eye enucleation was required. Eighteen patients developed ectropion of eyelids because of burn scar contracture. Thirteen patients underwent release of ectropion of the lids.

Pulmonary complications continued to be a significant cause of morbidity. There were 63 patients who were noted to have some type of inhalation injury documented either by bronchoscopy or xenon lung scan. This 24.2% incidence of all dispositions has remained constant when compared to the previous year. Other thoracic injuries were somewhat uncommon in our burn population and consisted of one patient with pulmonary contusion, two patients with crush injuries to the chest, and one patient with fractured ribs. The development of in-hospital pulmonary complications was relatively frequent and occurred most commonly in patients with an inhalation injury. Forty-five patients developed pulmonary edema and 42 patients developed bronchopneumonia, 33 of whom expired. Eighty patients at some time in their hospital course required mechanically assisted ventilation. These numbers document the continued high rate of serious complications among patients with inhalation injuries. Other complications related to inhalation injury consisted of atelectasis (18 patients) and acute respiratory obstruction (two patients). Other pulmonary complications not directly related to the presence of an inhalation injury included five cases of aspiration pneumonia, five cases of hematogenous pneumonia, and ten pleural effusions. Eleven patients developed pneumothorax which resolved with placement of thoracostomy tubes. Non-fatal pulmonary embolus occurred in seven patients. Seventeen patients had tracheostomy performed to facilitate prolonged mechanical ventilatory support.



As in past years cardiac complications were associated with a high mortality rate. Three patients sustained myocardial infarction in 1976. This incidence was lower than in previous years. The incidence of bacterial endocarditis also was decreased in 1976 with only three cases during the year. Other complications noted were one case of myocarditis, one case of pericarditis, and cardiomegaly in ten patients. There was an increased use of Swan-Gantz catheters both for measurement of pulmonary capillary wedge pressure and for determination of cardiac output. Catheters were placed to aid clinical management in 16 patients during 1976.

The number of gastrointestinal complications continued to decrease, and there continued to be a change in the type of complication seen. The number of patients having any type of gastrointestinal hemorrhage decreased from 60 patients in 1975 to only 29 in 1976 (an incidence of 11%). The majority of patients had either minimal bleeding through their nasogastric tube or guaiac positive stools. Clinical evaluation of patients with significant gastrointestinal hemorrhage demonstrated four gastric ulcers, one duodenal ulcer, and three stress ulcers. All cases of G.I. bleeding resolved with medical management and no operative intervention was needed in any of the patients. The 27 other esophageal and gastric complications which were noted consisted of esophagitis (4), gastritis (5), esophageal erosions (10), esophageal ulcers (4), and gastric infarction (3). Four patients who developed the superior mesenteric artery (SMA) syndrome were successfully treated nonoperatively. This further suggests that conservative therapy is the treatment of choice in patients who develop the SMA syndrome. Three cases of cholecystitis were diagnosed and all patients were treated successfully without operation. Four cases of pancreatitis were diagnosed in 1976 and all were successfully treated utilizing medical management. A moderately high incidence (14%) of hepatic complications continues with 36 patients having such abnormalities. Those patients with hepatomegaly who were autopsied usually exhibited cellular hyperplasia of the liver. Fatty liver was seen in four, central lobular necrosis was seen in five, chronic hepatitis was noted in one, alcoholic cirrhosis was noted in one, hemangiomas were noted in three, and only one patient was noted to have a liver abscess.

The renal problems seen in the patients in 1976 were usually associated with terminal status and often related to sepsis. There were 38 cases of renal failure for an incidence of 14.5%. Five patients underwent hemodialysis and one patient underwent peritoneal dialysis, none of whom survived. Abnormalities noted on autopsy specimens included 18 cases of cortical edema, 11 cases of congestion, four cases of cortical infarcts, and one case of cortical necrosis. Five patients developed urinary tract infections, and were successfully treated with antibiotic therapy.

Most endocrine problems were discovered at autopsy. One case of adrenal insufficiency was diagnosed in a patient who was treated with

steroids but went on to die of infection. Postmortem examination disclosed 12 cases of adrenal hemorrhage, 12 cases of adrenal congestion and one case of adrenal necrosis. Three cases of chronic thyroiditis were found and one pineal gland cyst was discovered.

Orthopedic complications were usually secondary to orthopedic injuries received at the time the burn occurred. Seventeen patients were admitted with fractures. There were four cases of malunion of fractures, and 11 cases of exposed bone which developed during the hospital course. Eight of these patients had to have operative debridement of dead bone to viable cancellous bone to allow the formation of granulation tissue for skin grafting. Four cases of osteomyelitis were noted and all were treated successfully with antibiotics. One patient developed myositis ossificans of the hip and one patient developed ectopic calcification in the area of the elbow.

Serious central nervous system complications were uncommon in our patients. Fifteen patients gave a history of having a loss of consciousness at the time of their accident. One patient had a subdural hematoma which was decompressed with placement of burr holes. Two patients with cerebral concussions and two patients with cerebral contusions were admitted during the year. Twelve patients had grand mal seizures during their hospital course. All episodes of seizure activity were relatively easily controlled with medications. Peripheral nerve injuries were most commonly associated with electrical burns. In 1976 there were three ulnar nerve injuries, two median nerve injuries, one radial nerve injury, one brachial plexus injury and one sciatic nerve injury. Three peroneal nerve injuries with two cases of foot drop occurred because of prolonged bed rest. Many significant psychological problems occur in burn patients and the routine visits by the Brooke Army Medical Center psychologist about three times a week were beneficial and resulted in resolution of most of these problems. Only two patients developed overt psychoses requiring consultation from the psychiatrists at Brooke Army Medical Center.

Only three pregnant women were admitted during 1976. Complications of these occurred in two patients. One patient aborted an immature fetus and one delivered a stillborn fetus.

Serious metabolic problems were uncommon. Only nine patients with diabetes mellitus were admitted to the burn unit in 1976. In general diabetes has been noted to be somewhat difficult to manage in the acute burn patient often requiring frequent blood sugar determinations and frequent administration of regular insulin in small doses or even carefully regulated continuous insulin infusion. A more conscientious effort to provide adequate caloric support was made and only four patients suffered massive weight loss in 1976.

## STATISTICAL RESUME

During the year 1976 257 thermally injured patients were admitted to the Institute of Surgical Research. There were 260 dispositions during 1976 and the subsequent data will be based on those dispositions. The patients ranged in age from 6 months to 86 years with 210 males and 50 females. The average age of the patients was 30.5 years with an average burn size of 38.3% total body surface and a 15.2% total body surface average third degree component. The average burn index was 26.5. Out of 260 dispositions, 187 had third degree burns. Thirty-three patients were less than 15 years of age with an average age of 5 1/2 years. The average total burn size in the pediatric age group was 29.4% total body surface with a 12.2% total body surface third degree area. The burn index of those children was 19.8 total body surface. Of the 33 pediatric patients admitted, 20 or 60% of the admissions had some third degree burn.

The average hospital stay in 1976 was 43.5 days. When the convalescent leave for active duty military personnel was excluded the average hospital stay was 37 days. The average postburn day for admission to the Institute of Surgical Research was 2.5 days. This figure reflects a continuing steady decrease of the time interval between injury and admission which in 1970 was 11.2 days. This change in the admission time over the past years reflects the fact that the vast majority of our patients are referred from sites within the Continental United States and our earlier receipt of requests for transfer. It also reflects the rapid response of the 375th Air Evacuation Wing, United States Air Force and the United States Army MAST Helicopter Evacuation Units in our joint effort in air evacuation missions.

During the year 1976 1,269 operations were performed on 214 patients or approximately six operations per patient. Four hundred and twenty-seven anesthetics were administered to 135 patients for an average of three anesthetics per patient. There were a total of 842 ward procedures performed. Three hundred and four autografting procedures were carried out on 122 patients for an average of 2 1/2 autografting procedures required to cover each patient. Fifty-one patients had 193 applications of allograft skin for an average of 3.7 applications per patient. The above figures are consistent with those for recent years except for a significant increase in the amount of allografting performed. Cadaver allograft skin was aseptically harvested from 74 cadavers, an increase from the 60 cadavers harvested in 1975.

Porcine cutaneous xenograft was applied to 38 patients 82 times for an average of two times per patient. This threefold increase over previous years in applications of porcine xenograft is attributed to increased use of biologic dressings in preparing wound beds for autografting. There were 50 patients who had escharotomies performed during 1976 or 19.2% of all dispositions. Nineteen major amputations were performed on 14 patients during 1976 and these were usually for treatment of severe



electrical injuries. Tracheostomy was performed in 17 patients or 6.5% of all dispositions, a number basically unchanged from recent years.

One hundred and eighty-five patients or 71.2% of all dispositions had at least one blood culture drawn during their hospitalization and 110 patients had one or more positive blood cultures. Seventy-six patients or 29% of all dispositions in 1976 had at least one burn wound biopsy performed. More data on the infections occurring in burn patients can be obtained in the 'Complications' section.

A total of 519,195 milliliters of blood were administered to 152 patients or 58.5% of all dispositions. This was an average of 3,416 milliliters of blood given to each of the 152 patients receiving transfusions. Eight of these patients (5.3%) had blood transfusion reactions. Only one of these reactions was felt to be hemolytic in nature and on further evaluation was found to be secondary to an ABO incompatibility.

Neither our admissions, the average burn size, nor the average hospital stay have significantly changed in the recent years, however certain characteristics of care have changed and need to be mentioned. In examining our census statistics there were 1,480 patient days in our Intensive Care Unit. This is an average of 4.05 patients each day in our Intensive Care. The low monthly census for the year occurred in September with 3.2 patients each day and the high average daily census was in March with 5.3 patients each day in the Intensive Care. On the Ward area of 14A there were 2,466 patient days or an average of 6.74 patients each day occupying ward space. On the convalescent ward, there were a total of 6,105 patient days or an average of 16.7 patients per day on the ward. The Respiratory Therapy Section has shown an increase in work load because of increasing use of mechanical ventilators. In 1976 there was a total of 4,970 ventilator hours for an average of 13.6 ventilator hours each day. In that year 6,235 IPPB treatments were administered. With our current trends in therapy we expect these numbers to increase significantly in 1977.

Table 1 identifies the source of admissions of patients during the calendar year 1976. The majority of patients were from the Continental United States. Twenty-nine patients or 11.1% were OCONUS. Table 2 summarizes the burn etiology in 1976. Gasoline and explosive volatile gases (natural gas, butane and propane) were about equally dangerous and were the cause of about 50% of the burns admitted to the Institute of Surgical Research. Burns caused by structural fires, explosive gases and ignition of clothing by cigarettes all had a high associated mortality approaching 50%. Table 3 summarizes the effect of age and total body surface injury on burn mortality. As expected the mortality increases with increasing age and extent of burn. In 1976 no patient with a burn greater than 80% of the body surface area survived. Table 4 lists the mortality rates associated with increments of 10% total body surface burn involvement for the years 1973 through 1976. This table shows a continued gradual improvement in survival of patients with



Table 1. Source of Admission, 1976

Area	A	AD	AF	AFD	N	ND	VAB	Other	TOTAL
1st Army	2	0	1	0	1	0	3	8	15
3rd Army	5	2	0	2	1	3	10	20	43
5th Army	10	7	6	9	5	1	26	90	154
6th Army	3	1	3	0	2	0	2	8	19
Peru	0	0	0	0	0	0	0	1	1
Alaska	1	0	0	1	0	0	0	2	4
Germany	2	2	0	0	8	0	0	0	12
Iran	0	0	0	0	0	0	0	1	1
Hawaii	0	0	0	0	2	0	0	2	4
Mexico	0	0	0	0	0	0	0	1	1
Guatemala	1	0	0	0	0	0	0	0	1
Okinawa	0	0	1	0	0	0	0	0	1
England	0	0	0	0	1	0	0	0	1
Puerto Rico	0	0	0	0	0	0	0	1	1
Panama	0	0	0	0	0	0	0	1	1
Greenland	0	0	0	0	0	0	0	1	1
	24	12	11	12	20	4	41	136	260

A - Army

N - Navy, Marine Corps &amp; US Coast Guard

AF - Air Force

VAB - Veterans Administration Beneficiary

D - Dependent

Other: Civilian Emergency

US Public Health Service Beneficiary

Bureau of Employees Compensation Beneficiary

Table 2. Burn Etiology, 1976 - 260 Dispositions

Causes	Number of Patients	%		Deaths	Mortality
		Disposition			
Gasoline & Kerosene	71	27.3%	24	33.8%	
Structural Fires	14	5.4%	6	42.9%	
Motor Vehicle Accidents	17	6.5%	4	23.5%	
Aircraft Accidents	15	5.8%	5	33.3%	
Open Flames	15	5.8%	5	33.3%	
Electrical	18	6.9%	1	5.6%	
Hot Liquid	25	9.6%	1	4.0%	
Chemical	1	0.4%	0	0.0%	
Others	13	5.0%	4	30.8%	
Butane, Propane or Natural Gas Exp.	55	21.2%	22	40.0%	
Welding Accidents	1	0.4%	0	0.0%	
Smoking Clothes Ignited	14	5.4%	7	50.0%	
Bomb, Shell, Simulator Grenade Exp.	1	0.4%	0	0.0%	
TOTAL	260		79		

Table 3. Age, Body Surface Involvement &amp; Mortality, 1976

Age (Yrs)	Per Cent Burn										Total		% Mortality
	0-10	10-20	20-30	30-40	40-50	50-60	60-70	70-80	80-90	90-100	Cases	Deaths	
0-1	1	1	1	0	0	0	1	0	0	0	4	0	0.0
1-2	2	3	1	1	0	1(1)	0	0	0	0	8	1	12.5
2-3	0	0	0	2	0	0	0	0	1(1)	0	3	1	33.3
3-4	1	0	0	1	0	0	0	0	0	0	2	0	0.0
4-5	1	0	0	0	0	0	0	0	0	0	1	0	0.0
5-10	1	3	0	0	0	0	0	1(1)	0	0	5	1	20.0
10-15	1	1	2	1	3	1	0	0	1(1)	0	10	1	10.0
15-20	2	4	6	3	4(1)	4(1)	6(4)	2(2)	1(1)	0	32	9	28.1
20-30	11	12	13	7(1)	8(1)	12(4)	8(5)	7(5)	5(5)	5(5)	88	26	29.5
30-40	3	12(1)	3	6(1)	4(1)	3(2)	4(3)	1(1)	1(1)	0	37	10	27.0
40-50	1	3	5(1)	2(1)	3(2)	2(2)	0	1(1)	2(2)	3(3)	22	12	54.5
50-60	2	7(1)	4(1)	6(1)	5(2)	3(2)	0	2(2)	1(1)	0	30	10	33.3
60-70	2	3	2	1	2(1)	1(1)	0	1(1)	0	0	12	3	25.0
70-80	0	0	1(1)	0	2(2)	0	0	0	0	1(1)	4	4	100.0
80-90	0	0	1	0	0	0	0	0	1(1)	0	2	1	50.0
Total	28	49	39	30	31	27	19	15	13	9	260		
Deaths	0	2	3	4	10	13	12	13	13	9		79	
% Mortality	0	4.1	7.7	13.3	32.3	48.1	63.2	86.7	100	100			30.4

Note: Deaths shown in parentheses.

Table 4. Per Cent Body Surface Involvement and Mortality, 1973 - 1976

% Burn	0-10	10-20	20-30	30-40	40-50	50-60	60-70	70-80	80-90	90-100	Total
(1973)											
No. Burned	39	35	46	26	38	32	20	16	12	9	273
Deaths	0	0	7	9	21	22	17	16	12	9	113
% Mortality	0	0	15.2	34.6	55.3	68.8	85	100	100	100	41.4
(1974)											
No. Burned	26	24	28	32	36	28	19	10	14	9	226
Deaths	0	0	4	10	18	17	17	9	13	9	97
% Mortality	0	0	14.3	31.2	50	60.7	89.5	90	92.9	100	42.9
(1975)											
No. Burned	20	36	29	42	28	28	34	19	13	5	254
Deaths	0	1	4	11	8	14	23	16	12	5	94
% Mortality	0	2.8	13.8	26.2	28.6	50	67.6	84.2	92.3	100	37
(1976)											
No. Burned	28	49	39	30	31	27	19	15	13	9	260
Deaths	0	2	3	4	10	13	12	13	13	9	79
% Mortality	0	4.1	7.7	13.3	32.3	48.1	63.2	86.7	100	100	30.4



Table 5. Per Cent Burn Versus Survival, 1955-1976

Year	Survivors (burns over 30%)			Deaths		
	No. Cases	Average % Burn Total	3°	No. Cases	Average % Burn Total	3°
1955	20	39.5	20.3	21	55.6	38.1
1956	22	41.0	17.3	20	57.8	37.8
1957	19	38.4	24.1	17	57.1	38.8
1958	15	42.3	21.6	23	56.5	35.3
1959	29	43.1	20.6	24	63.1	38.1
1960	17	44.2	20.1	30	57.8	37.3
1961	18	44.2	25.0	31	58.0	39.7
1962	18	42.7	21.4	54	59.1	46.2
1963	28	45.8	19.6	57	69.0	41.0
1964	40	41.8	14.8	37	65.0	42.4
1965	47	43.8	21.0	33	66.0	33.4
1966	68	41.5	14.9	59	59.9	31.3
1967	103	42.7	13.3	51	59.9	32.3
1968	143	44.2	12.6	38	54.6	24.6
1969	113	43.2	11.1	70	58.7	26.4
1970	92	39.4	10.7	70	51.9	32.6
1971	63	41.9	14.0	68	60.8	38.0
1972	62	42.0	17.2	103	56.7	35.9
1973	47	43.7	19.6	113	60.3	36.2
1974	55	43.9	12.2	97	60.87	35.9
1975	80	46.1	14.7	94	61.3	32.8
1976	69	45.5	15.0	79	64.2	31.1

Table 6. Comparison of Burn Mortality Rates, 1962-1963 and 1964-1976

Per Cent Burn																				
Years	0-30				30-40				40-50				50-60				60-100			
	No.	No.	%	Pts.	No.	No.	%	Pts.	No.	No.	%	Pts.	No.	No.	%	Pts.	No.	No.	%	
	Deaths Mortality				Deaths Mortality				Deaths Mortality				Deaths Mortality				Deaths Mortality			
1962-63	140	6	4.3	36	16	44.4	36	22	61.1	23	18	78.3	55	49	89.1					
1964-76	1804	55	3.1	535	95	17.8	454	144	31.7	302	150	49.7	550	468	85.1					

Table 7. Causes of Death, 1976.

Patient	Age	Sex	% Burn Total	PBD 3° Death	Cause of Death
1	46	M	99+	0	6 Renal failure secondary to acute tubular necrosis
2	40	M	95	90.5	12 Staphylococcal and Klebsiella septicemia originating in the burn wound
3	40	F	95	89	7 *Inhalation injury and Klebsiella sepsis
4	28	M	94	90	6 *Klebsiella sepsis originating in the burn wound
5	75	F	93.5	93.5	1 Cardiovascular collapse; inhalation injury
6	20	F	93	34	7 Pseudomonas and Klebsiella sepsis originating from the lungs
7	29	F	92	28	7 *Klebsiella sepsis
8	27	M	90	68.5	7 *Staphylococcal septicemia
9	21	F	90	22.5	5 Klebsiella septicemia
10	86	F	89.5	8	1 *Cardiovascular collapse
11	16	M	88	60.5	19 Pseudomonas sepsis from empyema left pleural cavity
12	22	M	86	57	25 Septicemia, organism Klebsiella, Pseudomonas and Staphylococcus
13	2	M	85	73	1 *Severe inhalation injury
14	40	M	85	0	5 Klebsiella sepsis originating from wound
15	45	M	84	81	17 *Klebsiella sepsis originating in the burn wound
16	31	M	83	35	11 *Klebsiella sepsis originating in the burn wound
17	12	M	82.5	37	17 Klebsiella and Pseudomonas sepsis arising in the burn wound
18	28	M	82	49.5	3 *Cardiovascular collapse possibly secondary to sepsis

\* Autopsy not performed

Table 7. Causes of Death, 1976

Patient	Age	Sex	% Burn Total	3°	PBD Death	Cause of Death
19	28	M	82	45.5	38	*Staphylococcal sepsis
20	21	F	82	22	5	Klebsiella sepsis arising in the burn wound
21	29	F	81	32	11	Klebsiella sepsis arising in the burn wound
22	55	M	80	59	8	Inhalation injury and acute myocardial infarction
23	61	M	79.5	23.5	5	Klebsiella sepsis
24	24	F	78.5	35	8	*Klebsiella sepsis arising from the burn wound
25	22	F	78	36	10	Severe inhalation injury
26	22	M	76.5	46	17	*Staphylococcal sepsis
27	36	M	75.5	31	8	Klebsiella sepsis arising in the burn wound
28	25	M	73.5	0	8	*Klebsiella sepsis arising in the burn wound
29	18	F	73	58.5	10	Severe inhalation injury and Klebsiella sepsis arising from the lungs
30	29	M	73	30	8	Klebsiella sepsis arising from the wound
31	56	M	72.5	40	6	Severe inhalation injury with attendant respiratory failure
32	40	M	70.5	15	16	Pseudomonas sepsis arising from the burn wound
33	6	F	70	48	20	Klebsiella sepsis arising in the burn wound
34	19	M	70	40.5	11	Staphylococcal sepsis arising from clot in the superior vena cava
35	58	M	70	16	8	*Klebsiella sepsis arising in the burn wound
36	16	M	69	59	15	*Staphylococcal sepsis

\* Autopsy not performed



Table 7. Causes of Death, 1976

Patient	Age	Sex	% Burn Total	3°	PBD Death	Cause of Death
37	19	M	68.5	10	6	Inhalation injury with Pseudomonas and Klebsiella sepsis arising in the lungs
38	15	M	68	35	7	Klebsiella sepsis arising in the burn wound
39	22	M	67	47	3	Severe inhalation injury
40	25	M	66.5	20	9	Klebsiella sepsis arising in the burn wound
41	26	M	66	59	27	Staphylococcal sepsis secondary to suppurative thrombophlebitis right arm
42	26	F	65	22	25	Pseudomonas sepsis arising from the burn wound
43	31	F	64	0	17	Klebsiella sepsis arising from the burn wound
44	19	M	61.5	28	24	Pseudomonas sepsis arising from the burn wound and lungs
45	31	M	61.5	3.5	17	*Pseudomonas sepsis arising in the burn wound
46	37	M	61	40	38	Severe bronchopneumonia organisms Pseudomonas and Klebsiella
47	27	M	61	32	20	Pseudomonas sepsis arising in the burn wound
48	28	M	59.5	55.5	17	Klebsiella sepsis arising from the burn wound
49	22	M	59	16	4	*Severe inhalation injury
50	43	M	58.5	20	5	*Inhalation injury
51	59	M	57.5	0	13	Extensive severe necrotizing terminal ileitis and colitis secondary to exacerbation of Entamoeba histolytica infection
52	22	M	56	6	3	Severe inhalation injury
53	17	M	55	54	2	Severe inhalation injury

\* Autopsy not performed

Table 7. Causes of Death, 1976

Patient	Age	Sex	% Burn Total	3°	P80 Death	Cause of Death
54	1 6/12	F	55	25.5	7	Gram negative sepsis, organism <i>Klebsiella</i> arising in the burn wound
55	35	M	54	31	23	*Massive pulmonary embolus
56	44	M	54	12	40	Staphylococcal sepsis arising in a thrombophlebitic left jugular vein
57	62	M	53	39	22	Gram negative sepsis, organism <i>Klebsiella</i> arising from the burn wound
58	29	M	53	22.5	21	* <i>Pseudomonas</i> sepsis arising in the burn wound
59	26	M	53	0	14	<i>Klebsiella</i> sepsis arising from the burn wound
60	50	F	51.5	28.5	24	* <i>Klebsiella</i> sepsis arising from the burn wound
61	53	M	48.5	7	8	<i>Pseudomonas</i> sepsis arising from the burn wound
62	78	M	48	48	1	Severe inhalation injury
63	19	F	48	0	23	<i>Pseudomonas</i> sepsis arising from the burn wound
64	55	M	45	45	30	Residuals of a severe inhalation injury
65	49	M	45	36	6	Severe inhalation injury
66	25	F	45	3.5	17	Severe bilateral pneumonia secondary to inhalation injury
67	66	M	43.5	42	1	Cardiovascular collapse secondary to aspiration pneumonia
68	45	M	41	6	11	<i>Pseudomonas</i> sepsis arising in the burn wound
69	32	M	40.5	8	2	Severe inhalation injury
70	76	M	40	40	0	*Severe inhalation injury and cardiovascular collapse
71	36	M	39	11	9	<i>Pseudomonas</i> sepsis arising from the burn wound

\* Autopsy not performed

Table 7. Causes of Death, 1976

Patient	Age	Sex	% Burn Total	3°	PBD Death	Cause of Death
72	40	M	38	15	4	*Severe inhalation injury
73	54	M	38	0	7	Staphylococcal sepsis
74	29	F	30.5	20	12	*Severe inhalation injury with bilateral bronchopneumonia
75	72	F	26	0	16	Acute myocardial infarction
76	44	F	25	0	11	Severe inhalation injury
77	58	F	20.5	10	10	Respiratory failure secondary to pulmonary hemorrhage and infarct in right lung
78	37	M	14.5	0	14	Massive pulmonary embolus
79	58	M	10.5	9	18	*Hepatic failure and hepatic encephalopathy

\*Autopsy not performed

burns involving 20 to 80 per cent of the body surface area. Table 5 details the survival and mortality rates of patients with greater than 30% burns in the calendar years 1955 through 1976. No significant changes in recent years are noted in this table. Table 6 shows a comparison of the burn mortality in the pre-topical antimicrobial years 1962-1963 with the cumulative index since 1965 during which time Sulfamylon and later silver sulfadiazine have been used. The addition of this year's mortality and survival statistics have not significantly changed the table which shows that current topical therapy has improved burn survival except in these patients with very extensive burns where it has had no effect.

#### SUMMARY

A total of 257 patients were admitted to the U.S. Army Institute of Surgical Research and 260 dispositions were made during calendar year 1976. Many of the early problems with fluid resuscitation and airway management have been satisfactorily resolved as evidenced by the extremely low mortality noted during the initial treatment period. Silver sulfadiazine has been continued as the initial burn wound topical agent. However, it appears that it is becoming less effective against gram negative organisms, and therefore a combination therapy utilizing silver sulfadiazine and Sulfamylon has been utilized with improved results in patients with suspected or established gram negative invasive infections. The incidence of heat and chemical-induced respiratory damage has not changed. Earlier nasotracheal intubation and aggressive use of mechanical ventilatory support has been utilized in the treatment of these patients. Infection continues to be the most common cause of mortality in thermally injured patients. Clinical research is being carried out with studies of early hemodynamic changes, burn wound care and infection in progress. The results of these clinical studies have advanced our understanding of post injury pathophysiology and led to improved care of the burned soldier.



## PRESENTATIONS

Pruitt BA Jr: The Hemodynamic Effects of Burn Injury. Louisiana State Univ, LSU Medical Center, New Orleans, LA 12 Jan 76.

Pruitt BA Jr: Round Table Session, Charity Hosp, New Orleans, LA 12 Jan 76.

Rosenthal A: Modern Burn Therapy. Medical Aspects of Advanced Warfare Course, USAF Sch of Aerospace Med, Brooks AFB, TX 14 Jan 76.

Sasaki TM: Treatment of Burns. Off Basic Course, Academy of Health Sciences, Fort Sam Houston, TX 19 Jan 76.

Pruitt BA Jr: Metabolic Changes in the Burn Patient. Symposium of Military Plastic Surgery, Walter Reed Army Medical Center, 21 Jan 76.

Peterson HD: Tangential Excision of Hand Burns. 9th Annl Symp of the Military Soc of Plastic Surgery, WRAIR, Washington, DC 21 Jan 76.

McDougal WS and Sinclair J: Careers in Surgery and Nursing. Students of Ed White Middle School, San Antonio, TX 23 Jan 76.

Pruitt BA Jr: 1) Resuscitation and Early Care, 2) Complications of Burns, Postgraduate Seminar in Surgery, 3) Art and Science in the Therapy of Difficult Problems in Surgery. Univ of Miami Sch of Med, Miami Beach, FL 21-24 Jan 76.

McDougal WS: Obstructive Renal Disease. Staff Nephrology Service, BAMC, Fort Sam Houston, TX 28 Jan 76.

Peterson HD: Tangential Excision of Hand Burns. South Texas Chapter American College of Surgeons meeting, Brownsville, TX 29 Jan 76.

Pruitt BA Jr: 1) Discussion of two papers. Moderator of Scientific Session and Chairman of Resident Award Committee. 30 Jan 76  
Report on ACS Board of Governors Mtg, 31 Jan 76. Brownsville, TX.

Wilmore DW: Nutritional Evaluation of Hospitalized Patients. Univ of TX Health Sci Ctr at San Antonio. 30 Jan 76.

Peterson HD: General Concepts in Burn Care. Burn Unit. Tulsa, OK 11 Feb 76.

McDougal WS: The Role of Research in Medicine and Surgery. Junior Science Engineering and Humanities Symposium. Univ of TX in Austin, 11 Feb 76.

Rosenthal A: Treatment of Burns. San Antonio Chapter Armed Forces Communications and Electronics Assn. Kelly AFB, TX 17 Feb 76.

Sasaki TM: Current Status of Burn Management. 7th Annual General and Family Practice Review. Portland, OR 17 Feb 76

Wilmore DW: Nutrition in Severe Catabolic Illness. Wilford Hall Medical Center, Lackland AFB, TX 6 Feb 76.

Kaplan JZ: Classification of Burns. ICU Nurse Clinician Course, BAMC, Fort Sam Houston, TX 18 Feb 76.

Kaplan JZ: Burn Wound Therapy. ICU Nurse Clinician Course, BAMC Fort Sam Houston, TX 19 Feb 76.

McDougal WS: Complications. ICU Nurse Clinician Course, BAMC, Fort Sam Houston, TX 23 Feb 76.

Rosenthal A: Hyperalimentation. ICU Nurse Clinician Course, BAMC Fort Sam Houston, TX 25 Feb 76.

Wilmore DW: Fat in Parenteral Nutrition. Massachusetts General Hospital, Boston, MA 24 Feb 76.

Pruitt BA Jr: 1) Current Concepts of Fluid Resuscitation. 2) Skin Grafting Techniques and Problems; 3) Nonbacterial Sepsis. ABA Seminar Univ of Washington Sch of Med, Seattle WA 26,27 Feb 76.

Wilmore DW: The Role of Fat and Carbohydrate in Parenteral Nutrition. Univ of Calif in San Francisco, San Francisco CA 28 Feb 76.

Pruitt BA Jr: Data from Studies and Clinical Use of Parenteral Fluid. Parenteral Alimentation Soc Mtg, Vail, CO 4-5 Mar 76.

Wilmore DW: Energy Cost of Post-Traumatic Gluconeogenesis. Parenteral Society Workshop, Vail, Col 5 Mar 76.

Sasaki TM: Current Concepts in Burn Care.

Pieniadz C: Nursing Care of the Burn Patient  
Nursing students, San Antonio College, San Antonio, TX 15 Mar 76.

Pruitt BA Jr: The Development and Contributions of the US Army Institute of Surgical Research. Fifth National Flame-Free Design Conf. Houston, TX 17-18 Mar 76.

Peterson HD: Burns. Medical staff 41st Combat Sq. BAMC. 22 Mar 76.

Wilmore DW: Nutritional Requirements in Burn Patients. Columbia University, New York, NY, 26 Mar 76.

The following presentations were made at the American Burn Assn  
Anl Mtg in San Antonio, TX 1-3 Apr 76

Pruitt, BA Jr; Multidisciplinary Care and Research for Burn  
Injury. (Presidential Address)

Rosenthal A: Gastrin Levels and Gastric Acidity Following Burns.

McAlhany JC Jr; Antacid Control of Acute Gastroduodenal Disease.

Peterson HD: Further Observations Prospective Comparison Study--  
Sulfamylon and Silver Sulfadiazine

Wilmore DW: Is Hepatic Dysfunction the Cause of Death in Septic  
Burn Patients?

Peterson JP: Nutritional Efficacy, Preparation, and Delivery of  
Oral Feedings to Severely Burned Patients.

Pruitt BA Jr: Discussor of two papers at Amer Surg Assn mtg, New  
Orleans, LA 6-9 Apr 76.

Wilmore DW: Mechanism of Thermogenesis Following Thermal Injury.

Aulick LH: Mechanisms of Glucose Calorigenesis

Symp on Thermogenesis, Federation Proceedings. Anaheim, CA 11 Apr 76.

Pruitt BA Jr: Treatment of Fungal Infections. ACS spring mtg,  
Boston, MA 26 Apr 76.

Pruitt BA Jr: Combat Casualty Care. Member of working group at  
NMRDC-ONR Tech Workshop on Combat Casualty Care, Warrenton, VA 27-28 Apr  
76.

Peterson HD: Early Treatment of Hand Burns with Emphasis on Tan-  
gential Excision and Enzymatic Debridement. Wayne County Medical So-  
ciety Detroit, MI 5 May 76.

Pruitt BA Jr: Hypermetabolism and Nutrition in the Burn Patient.  
Moderator of afternoon session symp on "Severe Thermal Injuries, A Con-  
tinuing Challenge. Burn Unit, Children's Hospital of Michigan and Wayne  
State Univ Sch of Med, Detroit, MI 5 May 76.

Wilmore DW: Nutrition and Metabolism Following Injury. Internation-  
al Congress of Critical Care Medicine. Pittsburgh, PA 8 May 76.

Wilmore DW: Use of Intravenous Fat Emulsion in Surgical Patients.  
Univ of Pittsburgh Sch of Med, Pittsburgh, PA. 8 May 76.

Peterson HD: Current Concepts in Burn Treatment. Burn Seminar  
Central Maine General Hospital. Lewiston, ME 10 May 76.

Pruitt BA Jr: 1) The History and Activities of the American Burn  
Assn; 2) Current Management of Patients with Thermal Injury. First Natl  
Symp on Traumatology, Baltimore, MD 9-11 May 76.

Wilmore DW: Nutritional Support of Patients with Infection. Subcommittee on Infection, National Research Council, Arley House, VA 12 May 76.

McDougal WS: Treatment of Burns, Interns, Bexar County Hospital, San Antonio, TX 13 May 76.

Pruitt BA Jr: Current Management of Burn Injury. NY Univ Med Ctr Sch of Med, New York 18 May 76.

Pruitt BA Jr: Newer Pathogens and Changing Patterns of Conventional Organisms. Vanderbilt Univ Sch of Med Symp on Infections 20 May 76.

McDougal WS: Treatment of Burns. Students from Brooks AFB, TX 25 May 76.

Levine BA: Burn Therapy. Pharmacy Students University of Texas Health Science Center, San Antonio, TX. 3 Jun 76.

Peterson HD: Current Concepts in Initial Burn Care. Department of Surgery University of Texas Health Science Center, San Antonio, TX 11 Jun 76.

Wilmore DW: Uses and Abuses of Parenteral Fat Emulsions. Southwest Texas Pharmacy Association, San Antonio, TX 15 Jun 76.

Pruitt BA Jr: 1) Resuscitation and Early Care of the Burn Patients; 2) Life-threatening Complications in the Burn Patient. Univ of Minnesota Critical Surgery Care Course, Minneapolis, MN 16-18 Jun 76.

Peterson HD: Temporary and Definitive Closure of the Burn Wound. AMA Postgraduate Course "The Total Care of the Burn Patient". Dallas, TX 26 Jun 76.

Wilmore DW: Post-Traumatic Metabolism in Burn Patients. American Medical Association, Dallas, TX 26 Jun 76.

Pruitt BA Jr: Attended AMA Meeting, Dallas, TX and participated as follows: 1) Course Director, Total Care of the Burn Patient. Federal and Military Section, 26 Jun 76 and 2) Presentation; Sepsis and Other Complications of Thermal Injury. 27 Jun 76.

McDougal WS: Burns--Assessment and Emergency Management. BAMC Interns AMIC-ER, Fort Sam Houston, TX 29 Jun 76.

Sasaki TM: Treatment of Burns. Officers Basic Course. Academy of Health Sciences, Fort Sam Houston, TX 26 Jul 76.

McDougal WS: Post Obstructive Diuresis. BAMC Nephrology Service Fort Sam Houston, TX 30 Jul 76.



Lescher TJ: Classification of Burns. Intensive Care Nurse Clinician Course students, BAMC, Ft Sam Houston, TX 2 Aug 76.

McDougal WS: Burn Wound Therapy. Intensive Care Nurse Clinician Course students, BAMC, Ft Sam Houston, TX 4 Aug 76.

McDougal WS: Complications of Burns. Intensive Care Nurse Clinician Course students, BAMC, Ft Sam Houston, TX 5 Aug 76.

Sasaki TM: Treatment of Burns. Officers Basic Course. Academy of Health Sciences, Fort Sam Houston, TX 9 Aug 76.

Levine NS: Hyperalimentation Therapy. Intensive Care Nurse Clinician Course students, BAMC, Ft Sam Houston, TX 12 Aug 76.

Lam V: Burns. Respiratory Specialist Class, BAMC, Ft Sam Houston, TX 20 Aug 76.

McDougal WS: Current Burn Therapy. Surgical Staff Wilford Hall USAF Hospital, Lackland AFB, TX 20 Aug 76.

Pruitt BA Jr: The Initial Management of the Burn Patient. General Surgery residents and staff, Wilford Hall Medical Center, Lackland AFB, TX 20 Aug 76.

Sasaki TM: Treatment of Burns. Officers Basic Course. Academy of Health Sciences, Ft Sam Houston, TX 23 Aug 76.

McDougal WS: Burns--Assessment and Emergency Management. BAMC Interns AMIC-ER, Ft Sam Houston, TX 24 Aug 76.

Peterson HD: Current Trends in Hand Burns. University of Texas Health Science Center, General Surgery staff, San Antonio, TX 1 Sep 76.

Sasaki TM: Treatment of Burns. Officers Basic Course. Academy of Health Sciences, Ft Sam Houston, TX 7 Sep 76.

Sasaki TM: Treatment of Burns. Industrial Nurses Assn. San Antonio College, San Antonio, TX 8 Sep 76.

Peterson HD: Current Concepts in Hand Burns. San Antonio Society of Plastic Surgery, San Antonio, TX 8 Sep 76.

Pruitt BA Jr: 1) Opportunistic Infections in the Badly Injured Patient; 2) Stress ulcerations. Visiting Professor, Univ of Indiana Coll of Medicine, Indianapolis, IN 9-11 Sep 76.

Pruitt BA Jr: Discussant of four papers American Assn for Surgery of Trauma Mtg. Colorado Springs, CO 15 Sep 76.

Wilmore DW: Parenteral Nutrition in Burn Patients. Symposium on Parenteral Nutrition, University of the Netherlands, Maastricht, Holland 18 Sep 76.

Wilmore DW: The Relationships Between Fat and Carbohydrate Calories. Symposium on Parenteral Nutrition, University of the Netherlands, Maastricht, Holland 18 Sep 76.

Pruitt BA Jr: The Role of the US Army in Burn Care in the United States. Army Pharmaceutical Management Course, Academy of Health Sciences, Ft Sam Houston, TX 20 Sep 76.

McDougal WS: Post Obstructive Diuresis. Surgical Staff Univ of Cincinnati Med School, Cincinnati, OH 20 Sep 76.

McDougal WS: Post Obstructive Diuresis. Surgical Staff Medical School at the University of Wisconsin, Milwaukee, WI 21 Sep 76.

Peterson HD: Current Trends in Hand Burns. Dept of Surgery, Univ of Texas Medical School at San Antonio, San Antonio, TX 21 Sep 76.

Pruitt BA Jr: 1) Current Concepts of Fluid Resuscitation of Burn Patients. Postgraduate Trauma Course 22 Sep 76. 2) Opportunistic Infections in Trauma Patients. 23 Sep 76. 3) Metabolic Responses and Nutritional Problems in Trauma Patients. 23 Sep 76. Visiting Professor, Univ of Texas Medical Branch, Galveston, TX.

McDougal WS: Post Obstructive Diuresis. Surgical Staff, Hershey Medical Center, Hershey, PA 23 Sep 76.

Treat RC: Inhalation Injuries. Surgical Staff, University of Kentucky Medical School, Lexington, KY 24 Sep 76.

Sasaki TM: Treatment of Burns. Officers Basic Course. Academy of Health Sciences, Ft Sam Houston, TX 27 Sep 76.

McDougal WS: Post Obstructive Diuresis. Surgical Staff, University of Vermont Medical School, Burlington, VT 28 Sep 76.

Wilmore DW: Nutrition in Burns and the Role of Fat Emulsions. Massachusetts General Hospital, Boston, MA 28 Sep 76.

Peterson HD: Tangential Hand Excision. American Society of Plastic and Reconstructive Surgeons annual mtg, Boston, MA 28 Sep 76.

Sasaki TM: Acute Phase Burn Wound Treatment.

Jesse NF: Rehabilitative Healing Phase of Burns. Physical Therapy students, Univ of Mississippi School of Medicine, Jackson, MS 30 Sep 76.

Sasaki TM: Current Burn Wound Treatment  
Roberts ML: Nursing Care of the Burn Patient  
Jesse NF: Physical Therapy in Burn Treatment  
Peterson JP: Nutrition and metabolism following thermal injury  
Students of the Incarnate Word School of Nursing, Incarnate Word College,  
San Antonio, TX 2 Oct 76.

Levine BA: Care of the Burn Patient. Surgical Staff, VA Hospital,  
San Diego, CA 5 Oct 76.

Peterson HD: Current Concepts in the Management of Thermal Injuries. Continuing Medical Education program, Elgin Surgeons, Ltd., Elgin,  
IL 12 Oct 76.

Pruitt BA Jr: 1) Burn Wound is Never Sterile. Scientific Session on Operating Room Environment. 2) Chemical Hazards and Injuries to Industrial Workers. Session on Trauma: Occupational Injuries in Farm and Industry. 3) Worker Saponified. Session on Successfully Managing the Spectacular Occupational Injuries. American College of Surgeons annual meeting, Chicago, IL 11-15 Oct 76.

Pruitt BA Jr: Metabolic and Septic Complications of Burns. General surgical staff and residents, Dept of Surgery, Wilford Hall USAF Med Ctr, Lackland AFB, TX 22 Oct 76.

Wilmore DW: Nutritional Support of the Injured Patient; CNS Response to Injury. Trauma Update Symposium, Albuquerque, NM 28-20 Oct 76.

Peterson HD: Current Burn Therapy - Recent Advances in Surgery. Assn of Military Surgeons of the US, 83rd Annl Mtg, San Antonio, TX 2 Nov 76.

Sasaki TM: Burn Care and Research. Summit County Medical Society mtg, Akron, OH 2 Nov 76.

Pruitt BA Jr: 1) Local Treatment of Burns. 2) Surgical Treatment and Skin Coverage of the Acute Face Burns. 3) Treatment of Acute Infection in the Burn Patient. International Teaching Course on the Current Treatment of Burns, Barcelona, Spain, 2-7 Nov 76.

Sirinek KR: 1) Selective Release of Gastric Inhibitory PolyPeptide by Some Actively-Transported, Structurally-Similar Carbohydrates and 2) The Portal Hypertensive Effect of Dopamine.

McDougal WS: Glucose Dependent Hepatic Membrane Transport in Non-Septic and Septic Thermally Injured Patients.  
Assn for Academic Surgery, annl mtg, Key Biscayne, FL, 2-5 Nov 76.

Peterson HD: The Treatment of the Burned Hand. Recent Advances in Burn Therapy. Brown University. Providence, RI, 10 Nov 76.

Jesse NF: Physical Therapy Management in Burn Patients  
Ford DT: Occupational Therapy in Burn Patients. Students of the OT/PT classes (Tri-Service) Academy of Health Sciences, Ft Sam Houston, TX 11 Nov 76.

Pruitt BA Jr: The Care of the Burn Patient. Visiting Professor, Evanston Hospital, Evanston, IL 17 Nov 76.

Pruitt BA Jr: Diagnosis and Treatment of Acute Ulceration of the Upper Gastrointestinal Tract in Burn Patients. Dept of Surgery, Northwestern Univ School of Medicine, Evanston, IL 17 Nov 76.

Wilmore DW: Nutrition in Burns. Symposium on the Nutritional Aspects of the Care of the Critically Ill. Southern General Hospital, Glasgow, Scotland. 17-18 Nov 76.

Sasaki TM: Emergency Treatment for Burns. Explorer Scout Troop, San Antonio, TX 19 Nov 76.

McDougal WS: The Need for Homograft Skin. Interns BAMC, Ft Sam Houston, TX 2 Dec 76.

Pruitt BA Jr: The Burn Patient. Cornell Univ Postgraduate Course, New York, NY, 2 Dec 76.

Peterson HD: 1) Complications in Fluid Management in Adults; 2) Complications of Dressings in Burn Wound Management; 3) Topical Antibiotics and Complications from their use; 4) The Management of Pulmonary Complications - Panel; 5) Some Special Problems in Adults. Burn Symposium "Avoiding and Treating Complications in Burned Patients" Harlem Hospital Center, New York, 4 Dec 76.

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Wilmore DW: Metabolic Aspects of Intensive Care. Postgraduate Assembly of Anesthesiology, New York, NY 7 Dec 76.

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ANNUAL PROGRESS REPORT

PROJECT NO. 3S1611102BS05-0Q, MILITARY BURN RESEARCH

REPORT TITLE: ANESTHESIOLOGY

US ARMY INSTITUTE OF SURGICAL RESEARCH  
BROOKE ARMY MEDICAL CENTER  
FORT SAM HOUSTON, TEXAS 78234

1 January 1976 - 31 December 1976

Investigators:

James K. Sims, MD, Major, MC  
Gary W. Welch, MD, Lieutenant Colonel, MC  
Barry Zimmerman, MD, Major, MC

Reports Control Symbol MEDDH-288(R1)

Unclassified



ABSTRACT

PROJECT NO. 3S1611102BS05-00, MILITARY BURN RESEARCH

REPORT TITLE: ANESTHESIOLOGY

US Army Institute of Surgical Research, Brooke Army Medical Center,  
Fort Sam Houston, Texas 78234

Period covered in this report: 1 January 1976 - 31 December 1976

Investigators: James K. Sims, MD, Major, MC  
Gary W. Welch, MD, Lieutenant Colonel, MC  
Barry Zimmerman, MD, Major, MC

Reports Control Symbol MEDDH-288(R1)

In the period covered in this report, 476 anesthetics were administered to 139 patients, an average of 3.43 anesthetics per patient. The average patient received three anesthetics, but several received more than 10, one of these patients receiving a total of 16 anesthetics.

The most commonly used anesthetic agent was Ethrane<sup>R</sup> (56%), followed by ketamine (16%), halothane (13%), and nitrous oxide (10%). Regional anesthesia was used for slightly more than 4% of anesthetic administrations.

No serious anesthetic related complications have occurred during this period of time.

Anesthesia

## ANESTHESIOLOGY

### PREOPERATIVE EVALUATION

Most burn patients are several days postinjury when first seen by the anesthesiologist. In the immediate postburn period, the time is used to gain abundant physiologic data from routine monitoring of various parameters: hematologic (hematocrit, electrolytes, liver and renal function tests), pulmonary (arterial blood gases, respiratory rate, daily chest x-rays), cardiovascular (blood pressure, central venous pressure, cardiac index measured by way of Swan-Ganz catheters), and renal (urine output, urine chemistry), in addition to the usual preoperative patient interview and physical examination.

All electrical injuries have a preoperative electrocardiogram performed to rule out possible myocardial damage.

### PREOPERATIVE PREPARATION

All patients are kept NPO after 2400 the day prior to surgery with the exception of patients with protected airways (intubation by some route plus tube feedings) and children, who may receive clear liquids up to five hours prior to surgery.

### PREMEDICATION

Most burn patients require some pain relief during the trip to the operating room, and most receive a narcotic such as morphine sulfate, 0.1 mg/kg, to a maximal dose of 10 mg, one hour prior to surgery. Glycopyrrolate (Robinal<sup>R</sup>), 0.005 mg/kg to a maximal dose of 0.2 mg, is used to dry secretions. Both of these medications are delivered intramuscularly.

Valium (PO) is used for sedation prior to regional anesthesia.

### FLUIDS

All fluids are changed to D<sub>5</sub>RL on arrival in the operating room.

### TYPES OF ANESTHESIA

The pattern of anesthetic administration has changed from previous years and involves a greater use of enflurane and a lesser use of ketamine. The reasons for this change will be discussed under individual agent headings.

TABLE 1. PRIMARY AGENTS - 1976

	<u>No. of Cases</u>	<u>% of Total</u>
Enflurane	266	56
Ketamine	78	16
Halothane	60	13
N <sub>2</sub> O	48	10
Regional	20	4.2
Other	4	0.8

1. Enflurane (Ethrane<sup>R</sup>)

Enflurane is a halogenated ether which has been commercially available for approximately the past four years. It has a rapid induction with good muscle relaxation. Biotransformation amounts to less than 2% of an inhaled dose, a fact which perhaps accounts for the few clinical toxic effects observed in spite of the fact that increased plasma fluoride ion concentrations have been observed after administration to patients taking hepatic enzyme inducing drugs.

2. Fluothane (Halothane<sup>R</sup>)

The use of halothane is avoided mostly for irrational reasons related to descriptions of possible rare hepatotoxicity in the literature. Previous studies at the Institute of Surgical Research show its repeated use to be safe in the thermally injured patient, and the National Halothane Study showed halothane to be the anesthetic with the best overall mortality rate. It is a smooth anesthetic, unsurpassed as an agent for pediatric patients. This anesthetic is mainly used now for asthmatics, patients with digitalis toxicity, and children.

3. Nitrous oxide

This agent must be used in concentrations of 65-70% with oxygen to assure patient lack of recall of the procedure; thus, it fails to meet the criterion of being able to provide high oxygen concentrations to the hypermetabolic burn patients. Pancuronium is the only relaxant used in conjunction with this agent. Succinylcholine has not been used for any purpose in this unit for more than two years.

#### 4. Ketamine

This agent is used both IM and IV to produce its characteristic dissociative state, with preservation of basal functions (breathing) and laryngeal reflexes plus secondary catechol stimulation of the cardiovascular system.

Unfortunately, ketamine shares with its parent compound, phencyclidine, the production of a high incidence of unpleasant hallucinogenic side effects. There seems to be a "batch" difference in ketamine, and that now possessed by ISR has an almost 100% incidence of these effects. Laryngospasm, airway obstruction, and regurgitation can occur with ketamine. Pronounced blepharospasm prevents its use in eye cases.

#### 5. Subanesthetic Ketamine

Subanesthetic ketamine (single dose 1.5-2 mg/kg IM) has seldom been used during this reporting period. Several factors limit the usefulness of this agent; the Hubbard tank restricts the use of intravenous administration at times, and only procedures with low projected blood loss are scheduled for the tank room.

Repeated use of ketamine may lead to a buildup of tolerance to the drug's beneficial effects. Larger and larger doses must be used, with sequential administration leading to a greater incidence of undesirable side effects.

Multiple anesthetic administrations, spaced closely together, interfere with the feeding schedule of patients, resulting in delayed wound healing.

It should be noted that large doses of narcotics are most definitely not used for tank procedures. The pain encountered is not of the type which is relieved by narcotics, and tank procedures are of short duration. Narcotic use provides little pain relief and may lead to postoperative respiratory depression.

Short, repeated painful procedures should be carried out with a minimum of sedation, to the limit of the patient's tolerance, and narcotic premedication should only be used in small doses. General anesthesia is required for procedures in which pain is not alleviated by minimum narcotic sedation.

#### 6. Regional Anesthesia

Regional anesthesia is generally considered one of the safest methods available, but its use in the thermally injured patient is



limited for several reasons: sepsis and infection of the skin over the site of injection are contraindications for use, and multiple-site operations also limit the practicality of this method.

#### MONITORING TECHNIQUES

##### A. CIRCULATION

1. Precordial and/or esophageal stethoscope
2. Peripheral pulse
3. Blood pressure, usually by Infrasonde,<sup>R</sup> but also may be by Riva Rocci method. Direct arterial lines have been used when necessary.
4. CVP
5. Swan Ganz catheter
6. ECG
7. Sponge weight
8. Urine output

##### B. RESPIRATION

1. Rate
2. Auscultation
3. Arterial blood gases

##### C. TEMPERATURE

Most cases now have a temperature monitor. Because of greatly increased radiation of heat, hypothermia is a serious problem. Several methods are employed to maintain body temperature during anesthesia:

1. Ambient temperature is maintained at 80-85°F. This is probably the most important of all things done.
2. The anesthetic gases may be heated and humidified.
3. A circle system may be used to minimize heat loss.

4. Radiant heat lamps.

5. A K-thermia heating blanket is used. It is probably used most effectively on children weighing less than 10 kg and in cooling febrile patients.

TABLE 2. OVERALL PATIENT DATA, USAISR (1966-1976)

Year	No. of Patients	No. Patients Anesthetized (ISR Only)	No. Patients Anesthetized No. Patients (x100)	Total Anesthetics (ISR Only)	Anesthetics No. Patients Anesthetized (x100)	Average Per Cent Burn
1966	311	181	58.2	713	3.94	30
1967	389	239	61.4	670	2.80	28
1968	389	259	66.6	794	3.07	30
1969	294	189	64.3	601	3.18	36
1970	321	198	61.7	497	2.51	30
1971	301	179	59.5	475	2.65	31
1972	301	183	60.8	575	3.14	34
1973	273	141	51.6	377	2.67	38.5
1974	226	123	54.4	380	3.09	41.57
1975	254	142	55.9	490	3.45	42.1
1976	277	139	50.2	476	3.43	37

TABLE 3. NATURE OF SURGERY, USAISR (PER CENT)

Procedure	1971	1972	1973	1974	1975	1976
Debridement and/or homograft	15.5	19.7	21.5	22.60	25.0	23.0
Autograft	52.9	51.3	52.6	56.9	51.0	53.0
Orthopedics	13.0	8.9	8.0	8.1	8.0	5.0
Ear (chondrectomy)	4.0	3.1	2.6	1.60	1.0	2.0
Eye and lid	3.8	0.7	1.8	1.60	2.0	3.0
Intra-abdominal	1.7	7.8	2.1	3.70	2.0	<1
Tracheostomy & bronchoscopy	4.6	6.6	6.6	1.80	<1	0
Other	4.4	1.9	4.8	3.70	11.0	13.0



RESEARCH AND TECHNOLOGY WORK UNIT SUMMARY				1. AGENCY ACCESSION <sup>a</sup>	2. DATE OF SUMMARY <sup>a</sup>	REPORT CONTROL SYMBOL DD-DR&E(AR)636	
3. DATE PREV. SUMMRY	4. KIND OF SUMMARY	5. SUMMARY SCTY <sup>a</sup>	6. WORK SECURITY <sup>a</sup>	7. REGRADING <sup>a</sup>	8. DISB'N INSTR'N	9. SPECIFIC DATA - CONTRACTOR ACCESS <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	9. LEVEL OF SUM A. WORK UNIT
76 10 01	D. CHANGE	U	U	NA	NL		
10. NO. / CODES <sup>a</sup>	PROGRAM ELEMENT	PROJECT NUMBER	TASK AREA NUMBER	WORK UNIT NUMBER			
a. PRIMARY	61102A	3S1611102BS05	00	090			
b. CONTRIBUTING	62774A	3S762774A820	00				
c. CONTRIBUTING							
11. TITLE (Precede with Security Classification Code) <sup>a</sup> (U) Alteration of Host Resistance in Burned Soldiers (44)							
12. SCIENTIFIC AND TECHNOLOGICAL AREAS <sup>a</sup> 003500 Clinical Medicine							
13. START DATE		14. ESTIMATED COMPLETION DATE		15. FUNDING AGENCY		16. PERFORMANCE METHOD	
76 10		Cont		DA		C. IN-HOUSE	
17. CONTRACT/GRANT a. DATES/EFFECTIVE: NOT APPLICABLE b. NUMBER: c. TYPE: d. KIND OF AWARD:				18. RESOURCES ESTIMATE a. PROFESSIONAL MAN YRS b. FUNDS (in thousands)			
EXPIRATION:				PRECEDING			
4. AMOUNT:				FISCAL YEAR			
5. CUM. AMT.				CURRENT			
				77 1.8 26			
				78 2.0 50			
19. RESPONSIBLE DOD ORGANIZATION				20. PERFORMING ORGANIZATION			
NAME: <sup>a</sup> US Army Institute of Surgical Research				NAME: <sup>a</sup> US Army Institute of Surgical Research			
ADDRESS: <sup>a</sup> Ft Sam Houston, Tx 78234				ADDRESS: <sup>a</sup> Ft Sam Houston, Tx 78234			
RESPONSIBLE INDIVIDUAL				PRINCIPAL INVESTIGATOR (Furnish SSAN if U.S. Academic Institution)			
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21. GENERAL USE				SOCIAL SECURITY ACCOUNT NUMBER:			
FOREIGN INTELLIGENCE NOT CONSIDERED				ASSOCIATE INVESTIGATORS			
				NAME:			
				NAME:			
22. KEYWORDS (Precede EACH with Security Classification Code) (U) Infection; (U) Neutrophil function; (U) Metabolism; (U) Rat model; (U) Antibiotics; (U) Immunostimulants; (U) Endotoxemia							
23. TECHNICAL OBJECTIVE, 24. APPROACH, 25. PROGRESS (Furnish individual paragraphs identified by number. Precede text of each with Security Classification Code.)							
23. (U) To define the basis of infection susceptibility in burned soldiers. To identify specific white blood cell dysfunction and establish the metabolic basis for such. To determine the effect of antibiotics on neutrophil function. Establish a burned rat model of granulocyte dysfunction. Examine the effect of immunostimulant drugs and metabolism altering drugs on rat granulocyte function.							
24. (U) The high susceptibility of burned rats to Pseudomonas infection will be investigated. Rat granulocyte function will be examined. The effects of immunostimulation on host resistance will be examined. The <u>in vitro</u> effects of antibiotics and stimulants will be examined in cells from burned humans.							
25. (U) 76 10 - 77 09 An <u>in vivo</u> defect in chemotaxis in burned rats has been established and conditions of purification and isolation of peripheral rat granulocytes have been established. Levamisole therapy is being investigated.							

<sup>a</sup> Available to contractors upon originator's approval.

DD FORM 1498  
1 MAR 68

PREVIOUS EDITIONS OF THIS FORM ARE OBSOLETE. DD FORMS 1498A, 1 NOV 68 AND 1498-1, 1 MAR 68 (FOR ARMY USE) ARE OBSOLETE.

ANNUAL PROGRESS REPORT

PROJECT NO. 3S1611102BS05-00, MILITARY BURN RESEARCH

REPORT TITLE: ALTERATION OF HOST RESISTANCE IN BURNED SOLDIERS

US ARMY INSTITUTE OF SURGICAL RESEARCH  
BROOKE ARMY MEDICAL CENTER  
FORT SAM HOUSTON, TEXAS 78234

1 October 1976 - 30 September 1977

Investigator:

Albert T. McManus, Jr., Captain, MSC

Reports Control Symbol MEDDH-288 (R1)

Unclassified

## ABSTRACT

PROJECT NO. 3S1611102BS05-00, MILITARY BURN RESEARCH

REPORT TITLE: ALTERATION OF HOST RESISTANCE IN BURNED SOLDIERS

US Army Institute of Surgical Research, Brooke Army Medical Center, Fort Sam Houston, Texas 78234

Period covered in this report: 1 October 1976 - 30 September 1977

Investigator: Albert T. McManus, Jr, Captain, MSC

Reports Control Symbol MEDDH-288 (R1)

A burned rat model of altered granulocyte function has been established. The 350 gram Charles River rat with a 60% full thickness burn has significant reduction in peritoneal granulocyte accumulation following casein injection. In the same animals, however, the absolute count of circulating neutrophils is significantly elevated. Thus, it appears that as in burned man, postburn neutrocytosis is also accompanied by chemotactic defects (1,2).

Methods have been developed to purify rat peripheral granulocytes. With a single centrifugation, rat blood was separated into three purified cell populations.

The technique uses a two density Hypaque Ficoll (HF) step gradient. Saline diluted whole blood (1:2) is layered onto HF at a density of 1.077 g/ml which has been previously layered onto HF at a density of 1.084 g/ml. The tube is then centrifuged at 800 xg for 20 minutes. Following centrifugation, four phases are observed. The top phase contains diluted plasma. A visible cell band at the plasma top HF interface contains the mononuclear cells and platelets. The third phase is a diffuse granulocyte band below the top HF step and above the erythrocyte pellet. The granulocyte band is removed with a pipette. The band contains greater than 95% granulocytic leukocytes and a variable but low contamination of RBC. Residual RBCs are removed by hypotonic lysis.

Glucose metabolism has been measured in purified rat peripheral granulocytes. Latex stimulation of hexose monophosphate activity of rat granulocytes has been standardized. Stimulated rat peripheral cells showed glucose oxidation increases similar to man, e.g., a sixfold rise from the resting state.

1. Sevitt S. Eosinophil and other leukocyte changes in burned patients with special reference to adrenocortical activity. Brit Med J. 1: 976, 1951.

2. Warden GD, Mason AD, Jr, Pruitt BA, Jr: Evaluation of leukocyte chemotaxis in vitro in thermally injured patients. J Clin Invest 54: 1061, 1974.

Work in progress includes examination of the metabolism of burned rat neutrophils; examination of in vitro chemotaxis with burned rat neutrophils and examination of the possible corrective effects of immunostimulatory drugs such as Levamisole.

Infection  
Neutrophil function  
Metabolism  
Rat model  
Antibiotics  
Immunostimulants  
Endotoxemia



RESEARCH AND TECHNOLOGY WORK UNIT SUMMARY				1. AGENCY ACCESSION <sup>a</sup>	2. DATE OF SUMMARY <sup>a</sup>	REPORT CONTROL SYMBOL DD-DR&E(AR)636	
3. DATE PREV. SUMM <sup>a</sup>	4. KIND OF SUMMARY	5. SUMMARY SCT. <sup>a</sup>	6. WORK SECURITY <sup>a</sup>	7. REGRADING <sup>a</sup>	8. DISSEM INSTR <sup>a</sup>	9. SPECIFIC DATA - CONTRACTOR ACCESS <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	
76 10 01	D. CHANGE	U	U	NA	NL	A. WORK UNIT	
10. NO. / CODES <sup>a</sup>		PROGRAM ELEMENT		PROJECT NUMBER		TASK AREA NUMBER	
a. PRIMARY		61102A		3S1611102B505		00	
b. CONTRIBUTING		62774A		3S762774A820		00	
c. CONTRIBUTING							
11. TITLE (Precede with Security Classification Code) <sup>a</sup>							
(U) The Study of Metabolism and Nutritional Effects of Burn Injury in Soldiers (44)							
12. SCIENTIFIC AND TECHNOLOGICAL AREAS <sup>a</sup>							
003500 Clinical Medicine							
13. START DATE		14. ESTIMATED COMPLETION DATE		15. FUNDING AGENCY		16. PERFORMANCE METHOD	
76 10		Cont		DA		C. In-House	
17. CONTRACT/GRANT Not Applicable				18. RESOURCES ESTIMATE		a. PROFESSIONAL MAN YRS	
a. DATES/EFFECTIVE:				b. PRECEDING		c. FUNDS (In Thousands)	
b. NUMBER <sup>a</sup>				FISCAL		77	
c. TYPE:				CURRENT		13.2	
d. KIND OF AWARD:				YEAR		78	
e. AMOUNT:						11.5	
f. CUM. AMT.						155	
19. RESPONSIBLE DOD ORGANIZATION				20. PERFORMING ORGANIZATION			
NAME <sup>a</sup> US Army Institute of Surgical Research				NAME <sup>a</sup> US Army Institute of Surgical Research			
ADDRESS <sup>a</sup> Ft Sam Houston, Tx 78234				Surgical Study Branch			
				ADDRESS <sup>a</sup> Ft Sam Houston, Tx 78234			
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TELEPHONE: 512-221-2720				TELEPHONE: 512-221-4733			
21. GENERAL USE				SOCIAL SECURITY ACCOUNT NUMBER:			
FOREIGN INTELLIGENCE NOT CONSIDERED				ASSOCIATE INVESTIGATORS			
				NAME:			
				NAME:			
22. KEYWORDS (Precede EACH with Security Classification Code)							
(U) Nitrogen balance; (U) Burn injury; (U) Temperature regulation; (U) Environmental control; (U) Protein metabolism; (U) Hormones; (U) Glucose metabolism; (U) Humans							
23. TECHNICAL OBJECTIVE, 24. APPROACH, 25. PROGRESS (Furnish individual paragraphs identified by number. Precede text of each with Security Classification Code.)							
23. (U) To identify the etiology and humoral mediators of postinjury hypermetabolism and altered thermoregulation in burned soldiers. To assess the nitrogen sparing of varied alimentation regimens. To define alterations and control of blood flow to the wound and other organs, and to determine the rate of nutrient delivery provided by that flow. To describe the effects of thermal injury on hormone production and on protein, glucose, and fat metabolism.							
24. (U) The controlled environmental chamber is used to study thermoregulation and altered heat loss following injury. Respiratory exchange gas is measured continuously by mass spectrophotometer and a canopy hood system. Limb plethysmography is employed to assess blood flow in extremities with and without burns. Arterial and venous concentrations of nutrients are assessed and, with blood flow, turnover rate determined. Hormonal mediators are determined in blood and urine and their relationship to the altered metabolism determined. Nitrogen balance is related to dietary hormonal and exercise regimens and to septic complications. The effect of burn injury on protein "flux" into the wound and total body turnover is determined in burned rats.							
25. (U) 76 10 - 77 09 Hypermetabolism cannot be altered by ambient heating and oxygen consumption cannot be accounted for by body temperature in awake, resting, or sleeping patients. Blood flow is increased to the burn wound, and the injured extremity selectively consumes glucose and produces lactate. The burned leg does not demonstrate reflex vasodilation when core temperature of the patient is elevated by total body heating.							

<sup>a</sup>Available to contractors upon originator's approval.

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1 MAR 66

PREVIOUS EDITIONS OF THIS FORM ARE OBSOLETE. DD FORMS 1498A, 1 NOV 65 AND 1498-1, 1 MAR 66 (FOR ARMY USE) ARE OBSOLETE.

ANNUAL PROGRESS REPORT

PROJECT NO. 3S1611102BS05-00, MILITARY BURN RESEARCH

REPORT TITLE: The Study of Metabolism and Nutritional Effects of Burn Injury in Soldiers (The Relationship Between Limb Blood Flow and Metabolism Following Thermal Injury in Soldiers)

US ARMY INSTITUTE OF SURGICAL RESEARCH  
BROOKE ARMY MEDICAL CENTER  
FORT SAM HOUSTON, TEXAS 78234

1 October 1976 - 30 September 1977

Investigators:

L. Howard Aulick, PhD, Major, MSC  
Douglas W. Wilmore, MD  
Arthur D. Mason, Jr., MD  
Basil A. Pruitt, Jr., MD, Colonel, MC

Reports Control Symbol MEDDH-288(R1)

Unclassified

# ABSTRACT

PROJECT NO. 3S1611102BS05-00, MILITARY BURN RESEARCH

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Total resting leg blood flow, measured by venous occlusion plethysmography; leg oxygen consumption; substrate turnover; and leg surface temperature were determined in 21 nonseptic burn patients and four normals. The patients studied during the second to third week postinjury sustained total body surface injuries averaging 45% (range 12-86%) and leg injuries of 35% total leg surface (0-82.5%). To integrate the peripheral metabolic and circulatory events with the systemic responses to injury, total body oxygen consumption, cardiac output, rectal and mean skin temperatures were also measured.

Leg blood flow and leg surface temperature generally increased with total burn size but did not correlate with cardiac output, total body oxygen consumption, or body temperature. However, leg blood flow was closely related to the extent of the leg burn ( $r^2 = 0.73$ ). To evaluate the metabolic determinants of the wound blood flow, patients were matched for burn size (40.5% total body surface in one group vs. 42%), resulting in similar systemic responses to injury (cardiac index  $7.8 \pm 0.7$  L/min/m<sup>2</sup> vs.  $7.5 \pm 0.8$ ,  $\text{VO}_2$   $204 \pm 12$  ml/min/m<sup>2</sup> vs.  $241 \pm 22$ , rectal temperature  $38.5 \pm 0.3^\circ\text{C}$  vs.  $38.3 \pm 0.3$ , NS). One group (n = 7) had extensive leg burns (58% of the leg surface), the other (n = 9) minimal leg injuries (9.5%). Leg oxygen consumption was similar in the two groups ( $0.24 \pm 0.01$  ml/100 ml leg·min vs.  $0.19 \pm 0.04$ , NS), although leg blood flow was markedly increased in the injured extremities ( $8.0 \pm 0.5$  ml/100 ml leg·min vs.  $4.2 \pm 0.4$ ,  $p < 0.001$ ). Glucose uptake and lactate production were enhanced in the burned extremities (glucose  $0.34 \pm 0.08$  mg/100 ml leg·min vs.  $0.04 \pm$

0.03,  $p < 0.01$ , lactate  $0.30 \pm 0.08$  mg/100 ml leg·min vs.  $0.06 \pm 0.06$ ,  $p < 0.05$ ) and related in a general manner with the size of the leg burn.

Increased peripheral blood flow following injury is directed to the wound and unrelated to aerobic metabolic demands of the extremity. The selectively perfused wound consumes glucose and produces lactate. The increased systemic cardiovascular and metabolic responses to thermal injury are essential for the enhanced circulatory and anaerobic demands of the healing wound.

Venous occlusion plethysmography  
Peripheral blood flow  
Oxygen Consumption  
Glucose and lactate turnover



## THE RELATIONSHIP BETWEEN LIMB BLOOD FLOW AND METABOLISM FOLLOWING THERMAL INJURY IN SOLDIERS

Circulatory and metabolic alterations characterize the compensatory adjustments which occur following major injury. After successful resuscitation, cardiac output rises and body temperature and ventilation increase, reflecting heightened energy demands on the body. Weight loss and increased urinary excretion of nitrogen, potassium, phosphorus, and other intracellular constituents, reflect the accelerated catabolism which occurs following trauma. During the hypercatabolic, reparative, or "flow" phase of injury, these general systemic events occur as if in response to tissue inflammation and in support of wound repair.<sup>1</sup> With healing of the wound, the systemic responses abate and convalescent anabolism begins, as characterized by an increased appetite and activity and a rebuilding of body mass.

Clinical studies over the past half century have quantitated and interrelated these systemic adjustments to injury. The initial observations of Cuthbertson, describing the post-traumatic responses following long bone fracture,<sup>2</sup> were confirmed and extended by Howard,<sup>3</sup> Moore,<sup>4</sup> and others. Although high caloric diets diminished loss of body tissue following injury,<sup>5</sup> the systemic hemodynamic and metabolic responses were not blunted by increased food

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3. Howard JE, Parson W, Stein KE, Eisenberg H, Reidt V: Studies on fracture convalescence. I. Nitrogen metabolism after fracture and skeletal operations in healthy males. *Bull Johns Hopkins Hosp* 75: 156, 1944.

4. Moore FD: *Metabolic Care of the Surgical Patient*. Philadelphia, W. B. Saunders, 1959.

5. Riegel C, Koop CE, Drew J, Stevens LW, Rhoads JE: The nutritional requirements for nitrogen balance in surgical patients during the early postoperative period. *J Clin Invest* 226:18, 1947.

intake.<sup>6</sup> The interrelationship between loss of protein economy and hypermetabolism was established by Kinney,<sup>7</sup> and associates<sup>8</sup> in a variety of surgical patients. The increase in cardiac output paralleled the rise in oxygen consumption in patients with various hypermetabolic disease processes.<sup>9</sup> Increased gluconeogenesis occurs in infected and injured patients,<sup>10</sup> and the rate of hepatic glucose production was closely related to the extent of injury.<sup>11</sup> Finally, the hormonal mediators of these systemic responses to injury were recognized<sup>12</sup> and the central role of the sympathetic nervous system as orchestrator of the homeostatic events following major injury was established.<sup>13</sup>

Although the various systemic circulatory and metabolic alterations following injury have been quantified, it has been difficult to interrelate physiologic and biochemical events to each other and to the healing wound. In this study, associated systemic and regional hemodynamic and metabolic events were monitored in the thermally injured patient. The influence of the wound on these integrated physiologic responses was evaluated.

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## MATERIALS AND METHODS

### Subjects

Twenty one noninfected burn patients were selected to represent a wide range of total body surface and leg injuries; all were male, and none had known pre-existing diseases (Table 1). The patients were studied between the 7th and 22nd postburn day, with the mean day of study being the 13th day following injury. All patients were 1) normotensive and hemodynamically stable after an uneventful resuscitation, 2) in a normal state of hydration, with a hematocrit greater than 33, and without abnormalities in serum electrolyte concentration, osmolality, or pH, 3) free of systemic infection as determined by clinical symptoms and signs, chest x-rays, and daily blood cultures, and 4) alert, cooperative, and able to participate in the study.

Four normal subjects served as controls. All were thoroughly accustomed to the techniques of respiratory, circulatory, and metabolic testing.

### Subject Preparation

All subjects were studied in the early morning. Normal individuals fasted for at least 10 hours before the study, and all patients were fasted after midnight. Those patients requiring intravenous fluid to maintain a normal state of hydration received 0.04 molar nutrient-free sodium chloride infusions for six hours before and throughout the study. While routine clinical care continued, patient manipulation was minimized for at least six hours before the study. Patients who were unable to rest during this period were not studied.

The burn wounds were treated by a variety of techniques. The majority of patients were treated by the exposure method, utilizing silver sulfadiazene cream (Silvadene<sup>R</sup>) applied to the injured surface, but some patients were treated with 11% mafenide acetate topical antibiotic (Sulfamylon<sup>R</sup> cream). Some wounds were covered with dressings soaked in saline, 5% mafenide, or 0.5% silver nitrate. While the treatments themselves have no known direct effect on blood flow or leg metabolism, they do require manipulation of the patient, resulting in patient discomfort. To insure that each patient was well rested and unstimulated before the study, wound treatment was also minimized for at least eight hours prior to the study. In the patients treated by the closed technique, dressings were removed only from the left leg just prior to the study. Routine clinical care and monitoring were maintained throughout all phases of the study.

TABLE 1. Characteristics of Subjects Studied

Subjects	Age (Year)	Weight (kg)	Body Surface Area (m <sup>2</sup> )	Estimated* Total Leg Volume (L)	Total				Post- burn Day Studied	Individual Variations During Study
					Body Burn (Per Cent)	Per Cent Third Degree	Total Leg Burn (Per Cent)	Per Cent Third Degree		
Controls										
1	35	77.3	2.06	11.081	0	0	0	0	—	
2	24	75.0	1.98	12.442	0	0	0	0	—	
3	29	84.1	2.04	12.437	0	0	0	0	—	
4	28	63.6	1.72	9.602	0	0	0	0	—	
Patients										
1a	50	58.6	1.72	7.877	12	6	2.5	2.5	10	Measurement of left leg
1b	50	58.6	1.72	7.544	12	6	57.5	27.5	10	Measurement of right leg
2	36	80.8	1.99	12.042	12	1	0	0	10	
3a	29	83.5	2.06	12.500	24.5	0	20	0	11	
3b	29	83.5	2.06	10.567	24.5	0	20	0	18	
4	20	83.7	2.06	15.274	28	0	70	0	7	
5	32	89.4	2.05	13.146	29	5	2.5	0	9	Dressing on left hand
6	54	76.3	1.92	10.056	29.5	0	0	0	12	
7	18	69.6	1.91	9.306	35	1.5	10	0	11	
8	33	63.4	1.71	9.089	43	2	45	0	9	
9	40	88.0	2.10	13.229	45	24	17.5	5	12	Small venectomy wound left lower leg; upper extremities in dressings
10a	22	67.2	1.72	9.389	46.5	43	17.5	17.5	8	Dressings over trunk, both upper arms, and right thigh
10b	22	57.5	1.63	7.730	46.5	43	17.5	17.5	19	
11	19	72.8	1.92	10.022	48	2	12.5	0	12	
12	26	73.2	1.93	10.752	50	31	0	0	17	Dressings on right leg
13	18	80.3	2.07	12.799	50	40	82.5	82.5	22	Dressings on left upper extremity
14	28	77.2	1.97	10.769	50	14.5	52.5	15	21	Dressings on left hand
15	20	59.1	1.70	10.427	50.5	5	37.5	2.5	10	Two weeks post-excision; dressings on right leg
16	17	82.5	2.05	13.570	57.5	12	15	0	14	
17	19	68.2	1.91	8.635	61.5	28	60	57.5	21	
18	19	64.4	1.73	9.242	67	0	65	0	11	
19	21	67.2	1.78	10.930	73	2.5	45	0	15	
20a	24	61.1	1.70	9.873	78	0	80	0	11	
20b	24	53.4	1.61	6.622	78	0	80	0	20	
21	22	79.5	2.10	10.728	86	57	82.5	82.5	8	Dressings on arms and right leg

\* Volume of leg inside the plethysmograph (by displacement) plus volume outside.



### Study Design

All studies took place in an environmental chamber previously described.<sup>14</sup> The ambient temperature was maintained at 30°C and relative humidity ranged between 40-50%. Control subjects wore light cotton shorts, and patients were draped with a light cotton towel. The postabsorptive subjects were moved to the study room between 5:00 and 6:00 A.M. and placed supine in bed. Nine copper-constantan thermocouples were attached to the skin at the same sites in all subjects (dorsum of the foot, lateral and posterior calf, posterior and anterior thigh, dorsum of the hand, forearm, abdomen, and low back). Leg skin temperatures were monitored from both legs, using five additional thermocouples, in patients with asymmetrical leg burns. In those patients treated in dressings, the thermocouples were placed on the wound, under the dressing, except for the fully exposed leg under study. A rectal probe was inserted to a depth of 10 cm from the external anal sphincter. All temperatures were recorded at five-minute intervals on a Leeds and Northrup Numatron scanning facility and recorder. If not already present, an intravenous catheter was placed in a large caliber vein and patency maintained with a constant infusion of 0.04 molar sodium chloride solution. A plastic catheter (#25 or #21) was placed percutaneously in an accessible extremity artery (femoral, dorsalis pedis, or radial) not in the leg under study and positioned to insure free flow of arterial blood. Patency of the catheter was maintained by slow infusion of 0.04 molar sodium chloride by syringe pump.

Following the initial preparation phase, the patients were allowed to rest for at least an hour in the semidark, quiet room and then repositioned to the side of the bed. The left leg (both legs were studied on Patient 1) was inserted in a large, soft, pliable water-impermeable boot and then placed in a full-length plethysmograph. Water was added to the plethysmograph at a temperature equal to the mean leg skin temperature and maintained at that temperature throughout the remainder of the study. At the end of a 30-minute period of equilibration with the water in the plethysmograph, the subject's cardiac output was determined by the dye dilution technique. This was followed by measurement of leg blood flow and calibration of the plethysmograph. A canopy hood was then placed over the patient's head, and continuous oxygen consumption was measured over 15-20 minutes. Following this, blood was then drawn from the femoral vein and, simultaneously, from the arterial line for determination of arterial and venous substrate concentration of the limb under study. Water was then drained from the plethysmograph and the patient's leg removed from the instrument. In preliminary investigations, the order of these

14. Wilmore DW, Mason AD Jr, Johnson DW, Pruitt BA Jr: Effect of ambient temperature on heat production and heat transfer in burn patients. *J Appl Physiol* 38:593-597, 1975.

measurements was varied. These trials demonstrated that the study results were unaffected by the measurement sequence as long as adequate time was allowed for the patient to return to the resting state following each manipulation. Puncture of the vasculature of the limb under study always followed measurement of limb blood flow.

Total time for the study, including periods for equilibration, was three to four hours. The patients usually slept throughout this period of time. As patient comfort was a basic prerequisite in this study, whenever it could not be achieved, the study was discontinued. To achieve near basal conditions, conversation was minimized and hand signals were used between the investigators during the study.

### Study Methods

Leg blood flow was determined by use of a full-length, water filled, venous occlusion plethysmograph as previously described.<sup>15</sup> Briefly, this plethysmograph is a rigid, rectangular box made of clear plexiglass. To facilitate its use in injured limbs, it can be disassembled into three sections, a thigh plate and attached boot, a trough section with mesh sling to support the leg, and a full-length top. The patient's leg was slipped through a tailor made opening in the thigh plate and into a large, loose fitting polyvinyl boot. The boot served to form a freely expandable, watertight seal between the limb and the plethysmograph, preventing fluid exchange across the burn wound and minimizing contamination. The boot and thigh plate were advanced to the proximal thigh and the leg placed in the mesh sling of the plethysmograph. The three sections of the plethysmograph were then locked together and the box filled with water equal to the mean skin temperature of the leg under study.

Venous occlusion was accomplished by rapid inflation of a 10 cm wide tourniquet cuff placed as high on the upper thigh as possible. Occlusion pressure was varied for each subject to obtain a maximal rate of limb swelling. In some patients with burns on the thigh, a topical anesthetic (2% viscous lidocaine) was applied to the area under the tourniquet cuff to reduce pain resulting from inflation. With venous occlusion, the limb swells; and the change in limb volume causes water to rise in a chimney located on the top of the plethysmograph. The increase in column hydrostatic pressure was converted to an electrical signal, amplified and recorded. In order to avoid the initial inflation artifact, the rate of leg volume change between 4-10 seconds following venous occlusion was used to determine leg blood flow. In the majority of measurements, the response was linear during this time period.

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15. Aulick LH, Wilmore DW, Mason AD Jr, Pruitt BA Jr: Influence of the burn wound on peripheral circulation in thermally injured patients. *Amer J Physiol* 237:901-906, 1977.

The plethysmograph was calibrated periodically with the leg in place. The volume of the limb within the plethysmograph was determined by subtracting the volume of water in the plethysmograph from its known capacity. The 8-10 flow measurements were averaged and leg blood flow expressed in ml/100 ml leg volume per minute. In order to relate peripheral measurements with the systemic events in the same patient, the volume of the entire leg was estimated. The approximate volume of the leg outside the plethysmograph was calculated from measurements of the circumference of the exposed thigh and the distance from the symphysis pubis to the plethysmograph. Total leg volume estimates were used only in the comparison of total body and leg oxygen consumption; all other results reported in 100 ml units of leg volume utilized only the portion of the leg within the plethysmograph. The validity of including the proximal portion of the leg not within the plethysmograph in the total leg measurements was demonstrated by studies in normal subjects. Withdrawing the leg from the plethysmograph had no effect on leg blood flow per 100 ml leg volume until the instrument was below the mid-thigh level.

Cardiac output was performed by rapidly injecting a 1 ml bolus of indocyanine green dye (10 mg/ml) into a large bore vein and monitoring the arterial dilution with a Waters DCR-702 densitometer, strip chart recorder, and cardiac output computer. Each reported cardiac output was the mean of three to five determinations. Prior to each experiment, known concentrations of green dye were mixed with the subject's venous blood, and the densitometer and recorder system were calibrated. The results obtained from the cardiac output computer were routinely verified by manual integration of the recorded curves. These dye dilution cardiac output results compared favorably with those obtained by the Fick and thermal dilution techniques.

Oxygen consumption of the patient was measured using a modification of the open circuit technique. The patient placed his head in a clear plexiglass canopy hood, fitted with a pliable loose-fitting neck seal. Forty to seventy liters of room air were pulled through the box by an exhaust fan, insuring that all expired air exited through the exhaust opening. Due to individual differences in ventilation, flow rate was adjusted for each subject by altering the size of the exhaust port. Optimizing flow rate for each subject prevented accumulation of carbon dioxide within the head box while providing the necessary differential between input and exit gas concentrations for accurate determination. A bidirectional, low resistance turbine flowmeter\* continuously measured exit flow. Concentrations of carbon dioxide and oxygen in the exhaust gas were monitored continuously and inflow gas concentrations measured at discrete time intervals by a Perkin-Elmer

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\*Quantum Flowmeter, Quantum Dynamics, Inc., Tarzana, California. Calibration of this flowmeter was performed at the University of Colorado Engineering Laboratory, Boulder, Colorado.



mass spectrometer (Model MGA-1100). Analog signals from the flowmeter and mass spectrometer were continuously fed to a dedicated computer housed within the metabolic room.

The temperature and humidity of the exhaust gas were determined through the use of wet and dry bulb thermometers placed in the exhaust air stream. These measurements and barometric pressure were entered into a program of the dedicated computer, which continuously integrated flow rate and gas concentrations and corrected gas volume to standard conditions. This data retrieval and analysis system provided serial determinations of the patient's oxygen consumption, carbon dioxide production, respiratory exchange ratio, and metabolic rate. The time interval for these computations was set between 2-5 minutes. Multiple on-line metabolic determinations provided by this system clearly established the development of a steady state respiratory gas exchange and permitted convenient basal metabolic measurements in patients with facial burns or subjects who were asleep. Analysis of exhaust air collected in Douglas bags yielded results within  $\pm 3\%$  of the volume and gas concentrations obtained by the canopy hood system.

At the end of the study, blood was drawn from the femoral vein of the leg under study through a 19 gauge needle. Simultaneously, arterial blood was sampled from the arterial catheter. Heparinized arterial and venous blood was analyzed for pH and oxygen concentrations using a Corning 165 Blood Gas Analyzer. Simultaneous Co-oximeter<sup>R</sup> measurements of oxygen content were performed in over one-half of the samples and yielded comparable results. Whole blood glucose was measured by the glucose oxidase method<sup>16</sup> and lactate by an enzymatic technique.<sup>17</sup> Hematocrit and hemoglobin concentrations were determined on all samples. All samples were measured in triplicate and the average value reported.

#### Calculations

Total body mean skin temperature ( $\bar{T}_{sk}$ ) was calculated by appropriately weighting nine skin temperatures according to the estimated surface area being represented:

$$\begin{aligned}\bar{T}_{sk} = & 0.143 T \text{ anterior thigh} + 0.081 T \text{ posterior thigh} + \\ & 0.168 T \text{ lateral calf} + 0.105 T \text{ low back} + 0.140 T \text{ forearm} \\ & + 0.050 T \text{ dorsum of hand} + 0.315 T \text{ abdomen.}\end{aligned}$$

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16. Hall JW, Tucker DM: Automated determination of glucose with glucose oxidase and potassium furocyanide. Anal Biochem 26:12, 1968.

17. Ellis JP Jr, Cain SM, Williams EW: Rapid accurate analysis of blood lactate. USAF School of Aerospace Medicine, Brooks AFB, Texas, SAM-TOR63-49-1-8 (June), 1963.



Mean leg skin temperature ( $\bar{T}_{skl}$ ) was calculated in a similar manner from five leg skin temperatures:

$$\bar{T}_{skl} = 0.365 T \text{ anterior thigh} + 0.122 T \text{ posterior thigh} + 0.250 T \text{ lateral calf} + 0.083 T \text{ posterior calf} + 0.179 T \text{ foot.}$$

Leg substrate turnover and oxygen uptake were calculated:

$$\text{Turnover} = \text{flow} \times (\text{arterial concentration} - \text{femoral vein concentration})$$

## RESULTS

### Systemic Response to Injury

Cardiac output, total body oxygen consumption, rectal and mean skin temperature all increase in a general manner with the size of the total body surface burn, and may reach a plateau as the extent of injury exceeds 50% of the total body surface (Table 2,3). Because all these systemic responses increase with burn size, they can be generally related to one another (Fig. 1). A specific cause and effect relationship among these systemic variables, however, cannot be established since they all generally increase following injury and are related in a similar way with the extent of injury.

### Local Response to Injury

Mean leg skin temperature, leg blood flow, oxygen consumption, glucose uptake, and lactate production increased in a general fashion with the size of the leg burn (Table 4). Leg blood flow (LBF) increased in a curvilinear manner with the per cent of leg burn (% LB):  $\text{LBF, ml/100 ml leg} \cdot \text{min} = 2.990 + 0.1576 \text{ LB} - 0.0011\% \text{ LB}^2$ , ( $r^2 = 0.73$ ). Leg blood flow was also curvilinearly related to the mean leg skin temperature of the extremity ( $r^2 = 0.58$ ). Although leg oxygen consumption increased with the size of the leg burn, extremity blood flow correlated poorly with leg oxygen consumption ( $r^2 = 0.16$ ). The uptake of glucose and production of lactate were not significantly related to the oxygen consumption of the extremity.

### The Relationship Between Systemic and Local Responses to Injury

With the increase in the size of total body surface burn, there is a general increase in the size of the leg burn ( $r^2 = 0.43$ ). The increase in leg blood flow, however, was poorly related to total body surface burn ( $r^2 = 0.33$ ), cardiac index ( $r^2 = 0.18$ ), total body oxygen consumption ( $r^2 = 0.33$ ), rectal or total body mean skin temperatures ( $r^2 = 0.08$  and  $0.19$ ). Leg oxygen consumption also correlated

TABLE 2. Systemic and Peripheral Responses to Injury

Systemic Responses					Peripheral Responses				
Subjects	Cardiac Index (L/m <sup>2</sup> ·min)	Oxygen Consumption (ml/m <sup>2</sup> ·min)	Rectal Temp. (°C)	Mean Skin Temp. (°C)	Mean Leg Surface Temperature (°C)	Leg Blood Flow (ml/100 ml leg·min)	Leg Oxygen Consumption (ml/100 ml leg·min)	Leg Glucose <sup>†</sup> Turnover (mg/100 ml leg·min)	Leg Lactate <sup>†</sup> Turnover (mg/100 ml leg·min)
Controls									
1	2.92	127	37.1	34.3	32.6	2.02	0.065	0.040	0.129
2	3.52	130	37.0	34.7	33.7	2.84	0.162	0.057	0.014
3	3.99	130	36.8	34.3	33.9	2.50	0.063	0.200	-0.058
4	3.29	119	36.9	34.3	33.8	3.10	0.205	0.124	-0.152
Patients									
1a	3.80	144	36.7	35.2	34.0	2.95	0.077	0.118	0.003
1b	3.80	144	36.7	35.2	34.6	8.53	0.255	0.171	-0.128
2	5.30	161*	37.9	34.9	33.8	2.61	0.144	0.157	0.050
3a	7.43	184*	38.7	36.6	36.1	8.39	0.155		
3b	5.59	184*	37.7	35.8	35.2	7.05	0.215		
4	7.00	296	38.6	36.2	35.9	7.48	0.219		
5	7.87	207	38.0	36.2	36.2	4.60	0.341		-0.090
6	9.86	188	39.4	37.1	35.3	4.42	0.193	-0.092	0.009
7	7.34	170	37.8	35.7	34.2	3.50	0.077	0.044	0.022
8	8.63	217*	38.2	36.3	36.4	8.60	0.230	0.018	-0.032
9	6.43	197	38.1	35.7	33.9	4.04	0.185	0.516	-0.430
10a	11.69	226	39.4	37.1	36.8	7.07	0.322	0.081	-0.428
10b	8.04	177	39.3	37.0	35.8	3.24	0.062	0.000	
11	8.95	226*	39.6	35.7	35.7	4.48	0.128	-0.097	-0.003
12	7.84	230*	38.3	36.0	34.8	3.17	0.307	0.202	-0.108
13	5.92	211	38.3	36.0	34.7	9.68	0.200	0.000	0.051
14	7.68	230*	38.3	36.3	35.7	6.24	0.230	0.484	-0.455
15	8.93	279	38.7	36.3	35.9	6.36	0.265	0.000	-0.056
16	8.38	258	39.0	36.7	35.3	4.93	0.186	0.099	-0.407
17	10.24	309	39.6	36.5	35.2	9.24	0.279	0.554	-0.025
18	7.64	204	37.2	35.8	35.8	12.21	0.144	0.000	-0.527
19	10.50	247	38.7	35.7	36.2	6.82	0.350	0.000	0.073
20a	11.18	345	38.7	36.5	35.9	8.33	0.541	0.500	-0.142
20b	8.06	227	38.5	36.8	36.1	10.71	0.231	-0.107	-0.418
21	5.94	265	37.5	33.8	31.6	5.94	0.373	0.148	-0.030

\* Oxygen consumption predicted from burn size; † positive values indicate uptake, — indicates production. (See Appendix for arterial concentrations and individual A-V differences.)

TABLE 3. *The Effect of Total Body Surface Burn on the Systemic Responses to Injury (Mean and Range or S.E.M.)*

	Controls	Per Cent Total Body Surface Burn		
		<25	25-49	>49
Number of subjects	4	3	8	10
Number of studies	4	5	9	11
Age (years)*	29 (24-35)	38 (29-50)	30 (18-54)	21 (17-28)
Weight (kg)	75.0 (63.6-84.1)	76.6 (58.6-83.5)	74.2 (57.5-89.4)	69.6 (53.4-82.5)
Body surface area (m <sup>2</sup> )	1.95 (1.72-2.06)	1.96 (1.72-2.06)	1.89 (1.63-2.10)	1.87 (1.61-2.10)
Per cent total body burn	0	16 (12-24.5)	38 (28-48)	62.5 (50-86)
Postburn day studied	—	12 (10-18)	11 (7-19)	15 (8-22)
Cardiac index (L/m <sup>2</sup> ·min)	3.43 ± 0.22	5.53 ± 0.74	8.42 ± 0.54	8.39 ± 0.52
Oxygen consumption (ml/m <sup>2</sup> ·min)	126 ± 3	168 ± 10	211 ± 13	255 ± 13
Rectal temperature (°C)	37.0 ± 0.1	37.8 ± 0.4	38.7 ± 0.2	38.4 ± 0.2
Mean skin temperature (°C)	34.4 ± 0.1	35.6 ± 0.4	36.3 ± 0.2	36.0 ± 0.2

\* Age and burn size were considered only once in the description of group characteristics.

FIG. 1. Cardiac index can be related to the metabolic rate of the injured subjects. However, since both the hypermetabolic and hyperdynamic circulatory response increase with the extent of injury, a cause and effect relationship between the two responses cannot be established.

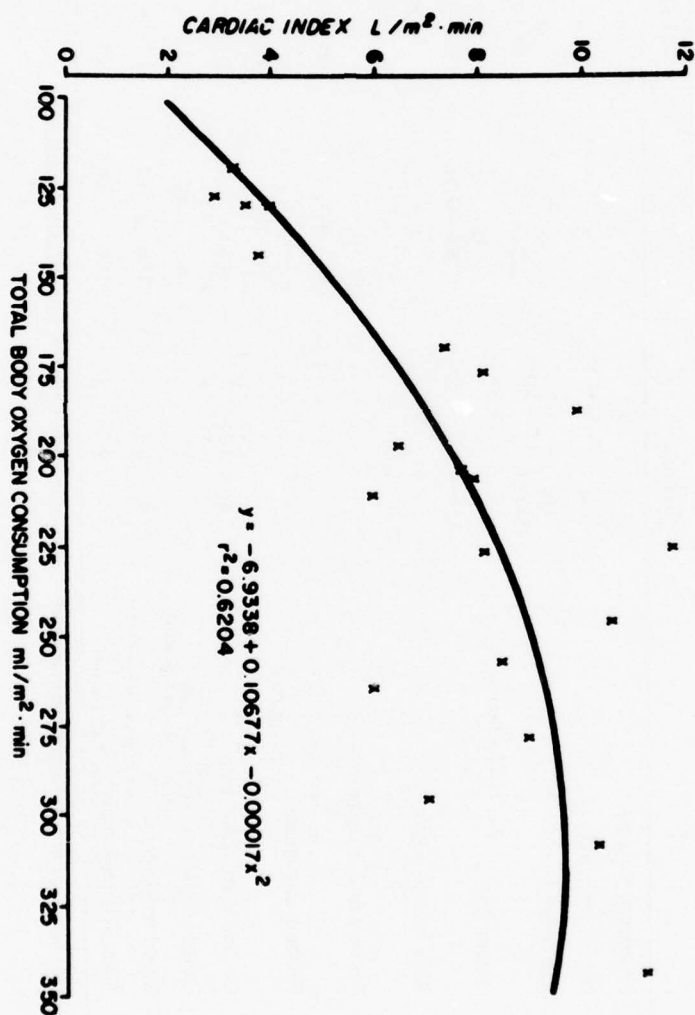




TABLE 4. *Effect of Leg Burn on Peripheral Circulation and Metabolism (Mean and Range or S.E.M.)*

	Control	Per Cent Total Leg Burn		
		<16	16-50	>50
Number of subjects	4	8	6	8
Number of studies	4	8	8	9
Age (years)	29 (24-35)	32 (17-54)	28 (20-40)	25 (18-50)
Weight (kg)	75.0 (63.6-84.1)	75.4 (58.6-89.4)	71.2 (57.5-88.0)	69.6 (53.4-83.7)
Body surface area (m <sup>2</sup> )	1.95 (1.72-2.06)	1.94 (1.72-2.05)	1.84 (1.63-2.10)	1.87 (1.61-2.10)
Per cent total body surface burn	0	34 (12-57.5)	47 (24.5-73)	54 (12-86)
Per cent total leg burn	0	5.5 (0-15)	30.5 (17.5-45)	69 (52.5-82.5)
Postburn day studied	—	12 (9-17)	13 (8-19)	15 (7-22)
Mean leg skin temperature (°C)	33.5 ± 0.3	34.9 ± 0.3	35.8 ± 0.3	35.1 ± 0.5
Leg blood flow (ml/100 ml leg·min)	2.62 ± 0.23	3.83 ± 0.31	6.45 ± 0.67	8.71 ± 0.68
Arterial O <sub>2</sub> content (ml/100 ml)	17.87 ± 0.14	15.43 ± 0.81	15.54 ± 0.54	14.37 ± 0.37
A-FV* O <sub>2</sub> difference (ml/100 ml)	4.51 ± 0.98	4.80 ± 0.92	3.49 ± 0.45	3.42 ± 0.61
Leg O <sub>2</sub> consumption (ml/100 ml leg·min)	0.124 ± 0.036	0.182 ± 0.035	0.223 ± 0.033	0.275 ± 0.039
Arterial glucose concentration (mg/100 ml)	75 ± 3	83 ± 3	101 ± 14	85 ± 5
A-FV glucose difference (mg/100 ml)	4 ± 1	2 ± 1	2 ± 1	3 ± 1
Leg glucose turnover (mg/100 ml leg·min) <sup>‡</sup>	0.105 ± 0.036	0.068 ± 0.033	0.126 ± 0.092	0.236 ± 0.083
Arterial lactate concentration (mg/100 ml)	11.6 ± 2.1	17.8 ± 3.3	16.9 ± 2.4	15.8 ± 2.9
A-FV lactate difference (mg/100 ml)	-0.1 ± 2.4	0.2 ± 0.5	-5.5 ± 2.2	-2.2 ± 0.7
Leg lactate turnover (mg/100 ml leg·min) <sup>‡</sup>	-0.017 ± 0.059	0.002 ± 0.018	-0.317 ± 0.105	-0.197 ± 0.071

\* Arterial-Femoral Vein.

‡ Positive values indicate uptake; - indicates production.

poorly with the body temperatures ( $r^2 = 0.13$  for rectal and  $0.04$  for mean skin) and cardiac index ( $r^2 = 0.28$ ) of the patients, but maintained a fairly constant relationship with total body oxygen consumption; the oxygen uptake of one leg accounted for approximately 6% of the total body oxygen consumption over the wide range of measurements (Fig. 2).

#### Local Factors Which Influence Peripheral Circulation and Metabolism

To standardize the systemic influences on peripheral events and thereby identify the local factors which influence leg blood flow, the patients were matched for age, weight, total body surface injury, and the associated systemic responses to injury (Table 5). One group had major leg burns (58% LB) and the other had minimal or no leg burns (9.5% LB). The systemic responses to injury were comparable in both groups, as reflected by similar body temperatures, cardiac index, and total body oxygen consumption. Leg blood flow, however, was increased significantly by the local presence of the burn wound. The increased leg blood flow was not associated with a comparable rise in limb oxygen consumption, indicating that the extra blood flow was not in response to increased aerobic metabolic demands of the limb. Glucose uptake and lactate production were higher in the more extensively injured limbs. In general, increases in glucose consumption and lactate production in the injured limbs were a function of both the increased leg blood flow and increased arteriovenous differences of these substances across the limb.

#### DISCUSSION

Previous indirect evidence suggests that much of the extra blood flow in the burn patient is directed to peripheral tissues. Gump and associates found that splanchnic blood flow represented a smaller proportion of the total cardiac output in three burn patients than it did in normal individuals or patients with postoperative infection.<sup>18</sup> Studies of body heat transfer in burn patients suggested that much of the peripheral blood flow was directed toward the surface. High superficial blood flow was apparent as burn patients maintained above normal surface temperatures in spite of increased evaporative cooling of the burn wound. In addition, the coefficient of core-to-skin heat conductance, an index of surface blood flow, was twice normal in burn patients studied in a variety of thermal environments.

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18. Gump FE, Price JB Jr, Kinney JM: Blood flow and oxygen consumption in patients with severe burns. *Surg Gynec Obstet* 130:23-28, 1970.

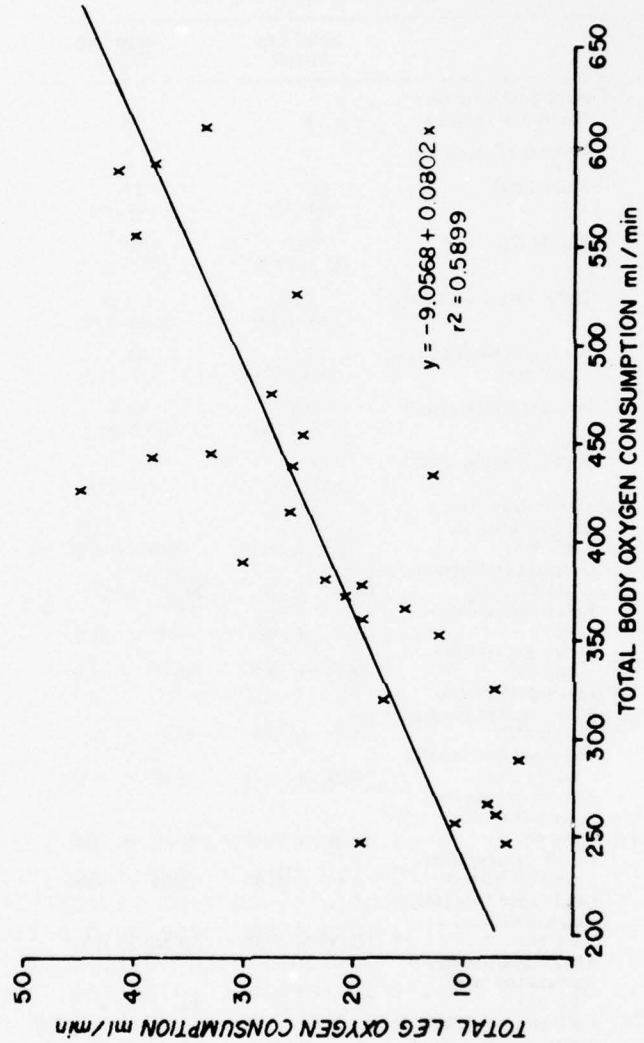


FIG. 2. The consumption of oxygen by the whole leg is related to total body oxygen consumption of the normals and hypermetabolic burn patients.

TABLE 5. Comparison of Patients With Small and Large Leg Burns (Mean and Range of S.E.M.)

	Small Leg Burns <sup>§</sup>	Large Leg Burns <sup>§</sup>
<i>Patient Characteristics</i>		
Number of subjects	8	7
Number of studies	9	7
Age (years)	28 (17-50)	27 (18-50)
Weight (kg)	73.2 (57.5-89.4)	70.1 (58.6-83.7)
Body surface area (m <sup>2</sup> )	1.89 (1.63-2.10)	1.88 (1.70-2.07)
Per cent total body surface burn	40.5 (12-57.5)	42 (12-61.5)
Per cent total leg burn	9.5 (0-17.5)	58.0 (37.5-82.5)
Postburn day studied	12 (8-19)	14 (7-22)
<i>Systemic Responses</i>		
Cardiac index (L/m <sup>2</sup> ·min)	7.82 ± 0.70	7.46 ± 0.81
Oxygen consumption (ml/m <sup>2</sup> ·min)	204 ± 12	241 ± 22
Rectal temperature (°C)	38.5 ± 0.3	38.3 ± 0.3
Mean skin temperature (°C)	36.1 ± 0.2	36.1 ± 0.2
<i>Peripheral Responses</i>		
Mean leg skin temperature (°C)	35.2 ± 0.3	35.5 ± 0.3
Leg blood flow (ml/100 ml leg·min)	4.22 ± 0.43	8.02 ± 0.51 <sup>‡</sup>
Arterial oxygen concentration (ml/100 ml)	15.08 ± 0.40	15.29 ± 0.72
A-FV <sup>¶</sup> oxygen difference (ml/100 ml)	4.40 ± 0.87	3.08 ± 0.26
Leg oxygen consumption (ml/100 ml leg·min)	0.187 ± 0.037	0.240 ± 0.010
Arterial glucose concentration (mg/100 ml)	89 ± 10	81 ± 4
A-FV glucose difference (mg/100 ml)	1 ± 1	4 ± 1*
Leg glucose turnover (mg/100 ml leg·min)	0.037 ± 0.033	0.336 ± 0.077 <sup>‡</sup>
Arterial lactate concentration (mg/100 ml)	17.2 ± 3.4	17.6 ± 3.6
A-FV lactate difference (mg/100 ml)	-1.4 ± 1.4	-3.6 ± 0.9
Leg lactate turnover (mg/100 ml leg·min)	-0.060 ± 0.055	-0.299 ± 0.075*

\*  $p < 0.05$ ; †  $p < 0.01$ ; ‡  $p < 0.001$ .

<sup>§</sup> Patient numbers 1a, 5, 7, 9, 10a, 10b, 11, 12, and 16.

<sup>¶</sup> Patient numbers 1b, 4, 8, 13, 14, 15, 17.

<sup>¶</sup> Arterial-femoral vein.



Since this data and the results of previous studies<sup>19</sup> demonstrate that increased leg blood flow in the burn patients is closely related to the extent of local injury on that particular extremity and not found in uninjured legs, the increased peripheral blood flow appears to be directed primarily to the burn wound. Wound blood flow is considered a major component of the hyperdynamic circulatory response to thermal injury. The increase in cardiac output is related to the extent of total body surface injury in a manner similar to the relationship between the size of limb injury and blood flow (Fig. 3). Serial blood flow measurements in patients with third degree wounds of the lower extremities further support the concept that this extra peripheral blood flow is wound directed. Two to three days after a full-thickness injury, which causes thrombosis of superficial vessels, leg blood flow is near control levels. With time, flow increases, and, by the end of the first week, reaches levels predicted for the size of the leg burn. This increase is associated with the formation of a richly vascularized wound bed. In contrast, partial-thickness injury does not ablate the superficial vascular bed, and blood flow is elevated in those legs with second degree burns as soon as circulatory volume is restored. In addition, excision of a vascularized full-thickness wound to fascia results in a prompt decrease in leg blood flow. Blood flow in these limbs is restored to elevated levels with formation of a granulation bed which will accept a skin graft.

Under normal physiologic conditions, blood flow to the extremity responds to variations in the oxygen demands of the limb and/or in response to thermoregulatory reflexes. The elevated leg blood flow observed in the burned limbs of our resting patients was not in response to an increase in the aerobic demands of the limbs, since no correlation could be established between extremity blood flow and oxygen consumption. Moreover, the high blood flow to the burned surface was not a thermoregulatory attempt to aid heat loss, for blood flow in the uninjured limbs of burn patients was normal, suggesting that these superficial vessels were vasoconstricted in a manner more appropriate to the heat conservation efforts of the febrile patients. However, leg blood flow was related to the size of the burn on the extremity, and patients with injured extremities also demonstrated an increased glucose uptake and lactate production in the burned limb. This is compatible with our knowledge of the morphology and biochemistry of the healing wound. Neovascularization is a constant

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19. Aulick LH, Wilmore DW, Mason AD Jr, Pruitt BA Jr: Peripheral blood flow in thermally injured patients. Fed Proc 36:788, 1977.

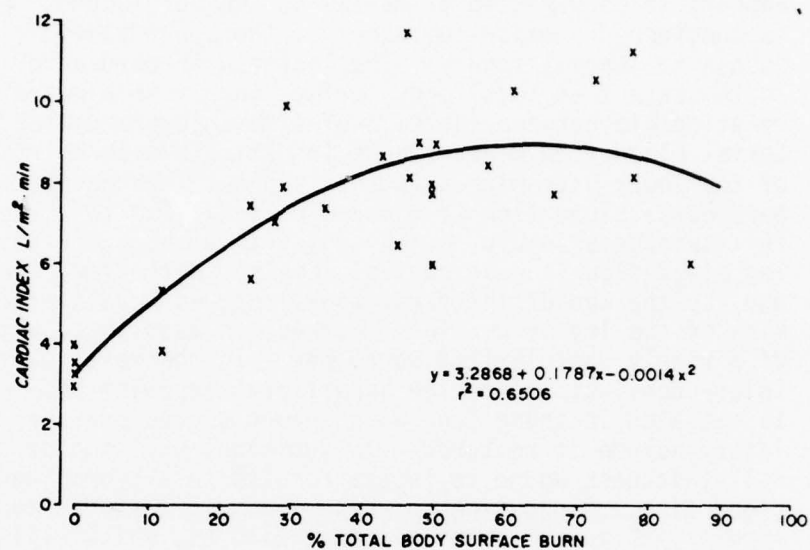
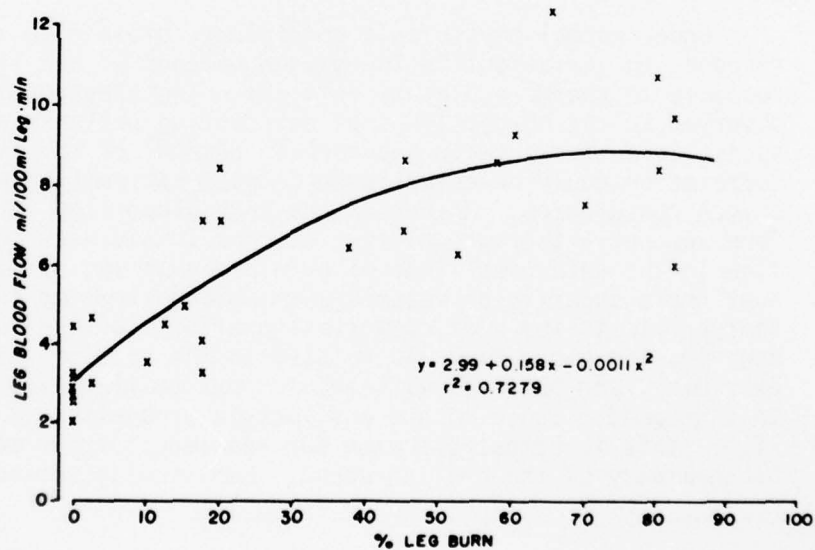


FIG. 3. Total body blood flow (cardiac index) is related to the extent of total body surface burn (top), in a manner similar to the relationship between leg blood flow and the size of the leg injury (bottom).



feature of wound repair,<sup>20,21</sup> and the development of granulation tissue in the open wound corresponds structurally with a dense, superficial, vascular bed. Although granulation tissue is highly metabolic, fibroblasts, leukocytes, and new epithelial cells are glycolytic and demonstrate a major capacity for anaerobic metabolism, especially when these cells are not located near the developing capillary network.<sup>22-25</sup>

Skin blood flow in normal individuals increases approximately five-fold if rectal temperature is artificially elevated to 38-39°C,<sup>26</sup> levels of hyperthermia comparable to rectal temperatures observed in these burn patients. However, leg blood flow in the uninjured extremity of hypermetabolic burn patients appears to be near normal levels. Previous evidence suggests an upward shift in the hypothalamic reference temperature of burn patients,<sup>27,28</sup> which would exert a reflex vasoconstrictor drive to the skin of uninjured limbs.

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20. Order SS, Moncrief JA: The Burn Wound. Springfield, Charles C. Thomas, 1966.

21. Zimmer JG, Demis DJ: Burns and other skin lesions: microcirculatory responses in man during healing. *Science* 140:994-996, 1963.

22. Cline MJ: Metabolism of the circulating leukocyte. *Physiol Rev* 45:674-720, 1965.

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26. Wyss CR, Brengelmann GL, Johnson JM, Rowell LB, Niederberger M: Control of skin blood flow, sweating and heart rate: role of skin vs core temperature. *J Appl Physiol* 36:726-733, 1974.

27. Aulick LH, Wilmore DW, Mason AD Jr, Pruitt BA Jr: Elevated central reference temperature following thermal injury. *Proceedings of the 27th International Congress of Physiology, Paris*, 13:37, 1977.

28. Wilmore DW, Orcutt TW, Mason AD Jr, Pruitt BA Jr: Alterations in hypothalamic function following thermal injury. *J Trauma* 15:697-703, 1975.

In addition, the high levels of circulating catecholamines observed in these patients<sup>29</sup> provide additional vasoconstrictor influences to the skin. Because the vasculature of the wound is relatively insensitive to reflex and circulating vasoconstrictor influences, peripheral blood flow is shunted away from uninjured skin and directed to the wound.

Although these total leg blood flow measurements are best related to increases in superficial blood flow, they do not allow partitioning of extremity blood flow into skin, muscle, connective tissue, and skeletal components. Thus, normal levels of blood flow to the uninjured extremity may be a reflection of increased muscle flow combined with decreased superficial flow, or simply normal superficial and deep flow. Muscle blood flow studies are now in progress to partition extremity flow. Shivering, or other limb movement observed in patients not included in this study, was associated with a marked increase in leg blood flow and oxygen consumption. This observation emphasizes the importance of environmental comfort to minimize energy and circulatory demands of the body during this hypermetabolic illness.

In this study, the rate of oxygen consumption was similar in burned and unburned extremities in patients with comparable total body oxygen consumption. Leg oxygen consumption in the normal and hypermetabolic patients accounted for an average of 5.6% of the total body oxygen consumption, a measured value similar to the estimates of 5.9% for normal man.<sup>30</sup> Moreover, the per cent or fraction of oxygen consumed by the leg was relatively constant over the wide range of total body oxygen consumption measured. This suggests that a systemic signal which controls total body oxygen consumption regulates the metabolic rate of the leg (i.e., skeletal muscle and possibly extremity fat). This generalized response accounts for the major oxygen demands of the extremity, and leg oxygen consumption is not significantly affected by the presence of a wound. This data, and rather limited information available on hepatic oxygen consumption in burned patients, suggests that the hypermetabolism associated with injury results from a systemic or generalized increase in aerobic metabolism. Partitioning the oxygen consumption in

29. Wilmore DW, Long JM, Skreen RA, Mason AD Jr, Pruitt BA Jr: Catecholamines: mediator of the hypermetabolic response to thermal injury. *Ann Surg* 180:653-668, 1974.

30. Stolwijk JAJ: Mathematical model of thermoregulation. In *Physiological and Behavioral Temperature Regulation*. J. D. Hardy, A. P. Gagge and J. A. J. Stolwijk, editors. Springfield, Charles C. Thomas, 703-721, 1970.



hyperthyroid patients yields similar results.<sup>31</sup> In contrast, the increased energy demands of exercise can be accounted for primarily by the increase in oxygen consumption of the active skeletal muscles.<sup>32</sup>

Increased glucose flow through the extracellular fluid compartment occurs in critically ill patients. Hepatic gluconeogenesis is increased in burn patients, and glucose flow was related to the extent of burn injury when the patients were studied during a time postinjury similar to the duration of this study. Glucose flow fell with time to normal levels in thermally injured patients with closure or healing of the burn wound. The present study demonstrates that peripheral utilization of this large quantity of glucose is principally confined to the wound. Net glucose uptake across the uninjured extremity is low, suggesting that fat, not glucose, is the primary fuel, a finding similar to that observed in normal man.<sup>33</sup> That fat is the major oxidized body fuel for the entire body is confirmed by the respiratory exchange ratio, which ranges between 0.70-0.76 in these and other injured patients.

It has been proposed that the cellular components of reparative tissue---fibroblasts, macrophages, leukocytes---which participate in the inflammatory response and mediate wound healing are glycolytic.<sup>34,35</sup> For example, it has been suggested that the energy required for collagen synthesis is derived from anaerobic glycolysis in the fibroblast.

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31. Kontos HA, Shapiro W, Mauck HP, Richardson DW, Patterson JL, Sharpe AR: Mechanism of certain abnormalities of the circulation to the limbs in thyrotoxicosis. *J Clin Invest* 44:947-956, 1965.

32. Rowell LB: Human cardiovascular adjustments to exercise and thermal stress. *Physiol Rev* 51:75-159, 1974.

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34. Chen RW, Postelthwait RW: The biochemistry of wound healing. *Monographs in the Surgical Sciences* 1:215-276, 1964.

35. Grant ME, Prockop DJ: The biosynthesis of collagen. *New Eng J Med* 286:291, 1972.

The lactate produced increases proline hydroxylase activity so the fibroblast can increase the rate of hydroxylation and collagen extrusion.<sup>36</sup> Studies of concentrations of glycolytic enzymes in granulating tissue support the concept that glycolysis is the most important source of energy in the open wound. While glycolysis and lactate production may occur in part because of an anaerobic environment, these reparative cells may have a predominant capacity for anaerobic metabolism independent of the local environment. For example, leukocytes and macrophages produce lactate in the presence of oxygen in response to phagocytosis. In addition, increased lactate production appears as a normal metabolic consequence of increased glucose utilization and may be related to the increased glucose consumption of the wound. Regardless of the precise mechanisms utilized by reparative tissue, glucose is consumed and lactate produced by the wound. This accounts for the conversion of six-carbon to three-carbon intermediates in the peripheral tissue of thermally injured patients, which would serve as a major source of gluconeogenic precursors following injury (via the Cori cycle).

Study of substrate balance to determine absolute turnover across the extremity is based on the assumptions that 1) an endogenous source of substrate does not exist in a storage form in the extremity, and 2) either uptake or production, but not both, occurs in the extremity under study. Although hepatic and muscle glycogen stores are depleted within the first several days following major injury, they may, in fact, be replenished by high-caloric feedings. Some muscle glycogen stores may exist in our patients at the time of study, especially in those individuals with small burn injuries who maintain a relatively large nutrient intake. If glycogen is present in the skeletal muscle, estimates of glucose uptake would be low. This effect, however, should be similar in the comparative groups of patients, with or without extremity injuries, that were matched for burn size and postburn day of study. Food intake and weight loss were also comparable in these two groups. In addition, lactate may not only be produced in the extremity but utilized by skeletal muscle as a specific fuel or alternative three-carbon precursor. But, once again, if these effects occur, they should be comparable in the matched patient study groups.

Substrate turnover measurements are based on the determination of concentration difference between arterial and venous blood samples. The

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36. Comstock JP, Wadenfriend S: Effect of lactate on collagen proline hydroxylase activity in cultured L-929 fibroblasts. *Proc Nat Acad Sci* 66:552, 1970.

differences in concentration of glucose and lactate across the leg were not great, and often approached the measurement error of the analysis. Therefore, multiple measurements were performed on each single sample, and the mean concentration of oxygen, glucose, and lactate determined. By comparing data from groups of patients with burned and unburned extremities, a mean arterial-femoral venous difference was calculated for each group. By minimizing individual variations, the general impact of the wound on substrate turnover becomes more apparent (see Table 5). The quantity of oxygen utilized by the extensively injured extremities is sufficient to account for oxidation of the quantity of glucose which is consumed by the burned legs. However, lactate is produced in the traumatized extremities, indicating that a portion of the glucose which is utilized in burned limbs is metabolized by anaerobic mechanisms. Calculated on a weight basis, the lactate produced accounts for a major portion of the glucose consumed by the extensively injured legs. Therefore, these data suggest that little or no oxygen is utilized for glucose metabolism in the extensively burned extremity. The oxygen consumed by the injured leg must be utilized to oxidize fat, which occurs primarily in the skeletal muscle. In the uninjured or minimally injured extremities, glucose consumption is minimal, suggesting that the major oxidized fuel in the uninjured extremities (primarily skeletal muscle) is fat. This *in vivo* evidence of glucose uptake and lactate production by the wound is similar to the *in vitro* data obtained in our laboratory when examining substrate turnover in biopsy samples taken from granulating wounds. In addition, this concept is also compatible with previous information describing the specific glycolytic capabilities of the specialized cells found in the healing wound.

This study demonstrates that glucose provides a specific fuel for cells involved in the inflammatory response and wound repair. Previous evidence suggests that increased gluconeogenesis occurs in burn patients,<sup>37</sup> and that the rate of hepatic glucose production is related to the size of the total body surface burn and oxygen consumption of the patient. That oxygen consumption and gluconeogenesis are interrelated is suggested by: 1) a decrease in both heat production and gluconeogenesis in burn patients during gram negative bacteremia, 2) a dose-related increase in heat production in normal man in response to glucagon infusion, which stimulates increased hepatic gluconeogenesis, and 3) a decrease in oxygen consumption in normals and burn

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37. Wilmore DW: Carbohydrate metabolism in trauma. *In* Clinics in Endocrinology and Metabolism 5:731-745, 1976.



patients following ethanol infusion, an agent known to block hepatic gluconeogenesis. In the trauma patient, body fat is oxidized to provide the energy necessary to support an increased rate of hepatic gluconeogenesis. Much of the glucose metabolized is converted to lactate and recycled; what glucose is oxidized is replaced by amino acids (primarily alanine), which arise from skeletal muscle and are transported to the liver to serve as additional gluconeogenic precursors.

This study reaffirms the priority of the healing wound in the body's response to injury. Glucose serves as a primary fuel for granulation tissue and is not utilized in the uninjured limbs. The glucose which is converted to lactate in the wound is recycled by the liver to new glucose. The energy required to support hepatic gluconeogenesis is most likely derived from fat, resulting in the production of both heat and glucose. The distribution of the peripheral circulation following thermal injury transports both heat and glucose preferentially to the wound. The energy cost of these reparative and transport processes is reflected in the increased metabolism and breakdown of body tissues and the hyperdynamic circulation. These systemic responses are essential for the support of enhanced circulatory and metabolic demands of the healing wound.

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Wilmore DW, Aulick LH, Mason AD Jr, Pruitt BA Jr: Influence of the burn wound on local and systemic responses to injury. Ann Surg 186:444-456, 1977.

#### PRESENTATIONS

Wilmore DW, Aulick LH, Mason AD Jr, Pruitt BA Jr: Influence of the burn wound on local and systemic responses to injury. Presented at the Annual Meeting of the American Surgical Association, Boca Raton, Florida, March 23-25, 1977.

# APPENDIX

## Arterial Concentrations and Arterial-venous Concentration Differences

	Oxygen		Whole Blood Glucose		Lactate	
	Arterial (ml/100 ml)	A-FV* Difference (ml/100 ml)	Arterial (mg/100 ml)	A-FV* Difference (mg/100 ml)	Arterial (mg/100 ml)	A-FV* Difference (mg/100 ml)
<b>Controls</b>						
1	18.00	3.21	73	2	16.8	6.4
2	18.12	5.72	76	2	6.6	0.5
3	17.88	2.51	83	8	12.8	-2.3
4	17.49	6.61	68	4	10.4	-4.9
<b>Burns</b>						
1a	16.58	2.62	68	4	15.2	0.1
1b	16.58	2.99	68	2	15.2	-1.5
2	20.04	5.51	88	6	19.1	1.9
3a	15.60	1.85				
3b	15.56	3.05				
4	14.29	2.93	94	5	9.9	-1.2
5	13.32	7.41	82	-2	6.0	0.2
6	13.78	4.37	99	1	13.5	0.5
7	17.02	2.19	86	0.5	13.2	-0.9
8	18.98	2.68	89	6	18.1	-5.0
9	15.52	4.57	170	2	9.9	-10.6
10a	15.28	4.56	84	0		
10b	15.29	1.91	70	-3	18.3	-0.1
11	14.36	2.86	86.5	4.5	25.8	-2.4
12	14.11	9.70	77	0	35.9	1.6
13	14.35	2.07	83	5	8.6	-4.7
14	15.20	3.69	75	0	36.5	-0.9
15	13.76	4.16	90	4	21.3	-6.4
16	14.21	3.78	80	2	13.5	0.5
17	13.89	3.02	68	6	13.4	-5.7
18	12.39	1.18	84	0	14.9	0.6
19	14.33	5.14	102	0		
20a	14.16	6.50	85	6	9.3	-1.7
20b	14.45	2.16	84	-1	20.9	-3.9
21	14.04	6.28	121	2.5	13.6	-0.5

Arterial-femoral vein



ANNUAL PROGRESS REPORT

PROJECT NO. 3S1611102BS05-00, MILITARY BURN RESEARCH

REPORT TITLE: The Study of Metabolism and Nutritional Effects of Burn  
Injury in Soldiers (Studies of Thermoregulation):  
Depressed Reflex Vasomotor Control of the Burn Wound

US ARMY INSTITUTE OF SURGICAL RESEARCH  
BROOKE ARMY MEDICAL CENTER  
FORT SAM HOUSTON, TEXAS 78234

1 October 1976 - 30 September 1977

Investigators:

L. Howard Aulick, Ph.D., Major, MSC  
Douglas W. Wilmore, M.D.  
Arthur D. Mason, Jr., M.D.  
Basil A. Pruitt, Jr., M.D., Colonel, MC

Reports Control Symbol MEDDH-288(R1)

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ANNUAL RESEARCH PROGRESS REPORT, 1 OCTOBER 1976-30 SEPTEMBER 19--ETC(U)  
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# ABSTRACT

PROJECT NO. 3S1611102BS05-00, MILITARY BURN RESEARCH

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Total leg blood flow was measured by venous occlusion plethysmography in five normals and 14 burned patients before and after 30 minutes of external heating. Leg surface temperatures were held constant, but rectal temperatures increased on the average of 0.4-0.5°C in all subjects following this heat load. Leg blood flow increased by 56.0% in the controls, 63.2% in five patients with essentially no leg burn (mean burn size = 1.5% leg surface), and 9.6% in nine patients with major leg injuries (mean burn size = 55% leg surface). Failure of reflex vasodilation in the burned leg was evident up to 107 days postinjury even when the wound was well healed. All subjects sweated freely from the unburned skin. In two patients, where arm and leg blood flows were measured simultaneously, flow to the uninjured arm increased while that to the injured leg remained unchanged. This lack of reflex vasodilation in the burned limbs, when appropriate vasomotor and sudomotor responses developed in the uninjured skin, suggests that wound vascular smooth muscle was denervated. This physical or chemical denervation could occur at the time of injury, be localized to the area of the wound, and result in loss of both neurogenic vasoconstrictor tone and active reflex vasodilation.

Wound blood flow  
Reflex heating  
Extrinsic control of cutaneous blood flow  
Skin trauma  
Innervation of skin neovasculature  
"Active" vasodilation of skin



## DEPRESSED REFLEX VASOMOTOR CONTROL OF THE BURN WOUND

The acute loss in plasma volume immediately following thermal injury results in an initial fall in cardiac output. During successful resuscitation, cardiac output begins to rise and may eventually reach levels 2-3 times normal in the more extensively injured patients. The hyperdynamic circulation accompanies a rise in resting metabolic rate and elevations in core and surface temperatures. Most of this extra blood flow appears to be directed to peripheral tissues, since splanchnic blood flow increases only slightly following burn injury. High surface temperatures, in the face of increased evaporative cooling of the wound, and twice normal rates of heat transfer from the core to the skin of burn patients, suggest that much of the increased peripheral blood flow is directed to the body surface. More recently, we have demonstrated that most of the elevated surface blood flow is directed primarily to the burn wound; blood flow to the uninjured legs of burned patients was essentially normal but increased in a curvilinear fashion with increasing leg injury.

This wound directed blood flow may be the result of 1) limited vascular smooth muscle development and intrinsic tone in the rapidly growing vessels of wound granulation tissue; 2) a traumatic loss of sympathetic vasomotor innervation, and/or 3) the presence of local vasodilatory metabolites in the wound which override neurogenic or circulating vasoconstrictor influences. Vascular smooth muscle tone is evident in the granulating wound, since blood flow to the severely burned leg increases appropriately when the surface of the injured limb is heated.

This study was designed to determine the capacity of the vessels in the burned wound to reflexly dilate when the surface temperature of the burned limb is held constant and the patient's central body temperature elevated by external heating.

### METHODS AND MATERIALS

Fourteen thermally injured patients, with a mean burn size of 38.5% of the total body surface, range 12-73%, and five normal individuals were studied (Table 1). The subjects' ages ranged from 19-56 years. Patients selected for study were 1) free of any pre-existing disease prior to injury; 2) normotensive and hemodynamically stable after an uneventful resuscitation; 3) in a normal state of hydration with an hematocrit greater than 33 and without abnormalities in serum electrolyte concentrations, osmolality, or pH; 4) free of systemic infection; and 5) able to participate in the study. The average size of leg burn was 36% of the leg surface, range 0-70%. Simultaneous arm and leg blood flow measurements were performed in two patients (patients 11 & 14) with burned legs and unburned arms.

TABLE 1. Subject Characteristics

Subject	Age (yr)	Body Surface Area (m <sup>2</sup> )	Postburn Day Studied	Burn Size	
				% Total Body	% Leg
<u>Controls</u>					
1	38	2.03		0	0
2	23	1.80		0	0
3	31	1.96		0	0
4	29	2.04		0	0
5	25	1.99		0	0
Mean	29	1.96		0	0
<u>Small Leg Burns</u>					
6	32	2.05	9	29	2.5
7	54	1.92	43*	29.5	0
8	55	2.11	11	35.5	0
9	34	2.10	27	38	5
10	23	1.79	13	39	0
Mean	40	1.99	21	34	1.5
<u>Large Leg Burns</u>					
11	50	1.72	25	12	57.5
12	19	2.18	68*	22.5	45
13	20	2.07	91*	28	70
14	56	1.99	75*	29.5	65
15	22	1.73	70*	41.5	45
16	22	1.74	73*	46	65
17	20	1.72	107*	50.5	37.5
18	19	1.73	11 & 26*	67	65
19	21	1.78	15	73	45
Mean	28	1.85	56	41	55

\* Wound healed, patient convalescing

The patients were studied from 9-107 days postinjury. Patients 6, 8, 9, 10, 11, 18, and 19 were studied early in their postburn course and had open leg wounds, but the other nine studies were performed on convalescent patients whose burn wounds were well healed. With the exception of patient 9, all unhealed wounds were treated by the exposure method. This involved topical application of silver sulfadiazine cream (Silvadene<sup>R</sup> cream) or 11% mafenide acetate topical antibiotic cream (Sulfamylon<sup>R</sup> cream) to the injured surface. Face, trunk, and upper extremity wounds of patient 9 were covered with dressings saturated in a 5% mafenide acetate solution. While these treatments have no known direct effects on wound blood flow, they do involve considerable manipulation of the patient, often resulting in discomfort. Therefore, to insure that each subject was well rested for the study, such procedures were minimized, whenever clinically feasible, for at least eight hours prior to the study.

Study Design. All experiments took place in the environmental chamber described previously. Room temperature was maintained at 30°C, and relative humidity ranged between 40-50%. The postabsorptive subjects, dressed in cotton shorts (controls) or appropriately draped with a light cotton towel (patients), rested supine in bed throughout the study. Nine copper-constantan thermocouples were attached to the skin at the same sites for all subjects (dorsum of foot, lateral and posterior calf, anterior and posterior thigh, dorsum of hand, forearm, abdomen and low back). In the one patient treated in dressings, thermocouples were placed on the wound under the dressings. A rectal temperature probe was inserted to a depth of 10 cm from the external anal sphincter. All temperatures were recorded at 5-minute intervals for at least one hour prior to the blood flow measurements to establish the development of thermal equilibrium. After the initial equilibration period, mean leg skin temperature was determined. The thermocouples were removed from that limb, and the leg was inserted into a large, pliable, water impermeable boot, and then placed in a full-length plethysmograph.

Water was added to the plethysmograph at a temperature equal to the predetermined mean leg skin temperature and maintained at this temperature throughout the remainder of the study. After a 30-minute equilibration period in the plethysmograph, 8-10 resting blood flow measurements were performed. A 1.5-2 minute period separated each blood flow determination. The subject was then heated with three radiant heat lamps for 30 minutes. Two sets of 3-4 leg blood flow measurements were performed; one beginning after 10 and the other after 25 minutes of external heating.

In the two studies where arm blood flow was measured, mean arm skin temperature was determined by using hand and forearm thermocouples, plus two others located on the anterior and posterior surfaces of the upper arm.



Blood flow measurements. Leg blood flow measurements were obtained through the use of a full-length, water filled, plethysmograph described previously. Briefly, this plethysmograph was a rigid rectangular box made of clear plexiglass. To facilitate its use in injured limbs, the plethysmograph can be disassembled into three sections; a thigh plate and attached boot; a trough section with a mesh sling to support the leg; and a full-length top. The subject's leg was slipped through a tailor-made opening in the thigh plate and into a loose-fitting, polyvinyl boot. The boot and thigh plate were then advanced to the proximal thigh and the leg rested in the mesh sling of the plethysmograph filled with water. The water was continuously stirred by two centrifugal pumps and its temperature maintained by circulating ethylene glycol from a thermostatically controlled reservoir through copper tubing located on the floor of the plethysmograph.

Using this apparatus, limb blood flow measurements required 10-15 seconds of venous occlusion. This was accomplished by rapid inflation of a 10 cm tourniquet cuff placed as high on the thigh as possible. In accordance with standard technique, cuff pressure was varied for each subject to obtain the highest rate of limb swelling. The increase in limb volume with venous occlusion caused water to rise in a chimney located on top of the plethysmograph. The rate of rise in column hydrostatic pressure was used to calculate arterial blood flow. Eight to 10 such flow measurements were averaged to establish mean, resting leg blood flow. The plethysmograph was calibrated with the leg in place after each 2-3 measurements. The volume of the limb within the plethysmograph was determined by subtracting the volume of water in the plethysmograph from its known capacity. Leg blood flow values are then reported in ml/100 ml of leg volume per minute.

In two patients, simultaneous arm and leg blood flow measurements were performed before and after external heating. The plethysmograph used on the upper extremity was of the same basic design as the leg plethysmograph described previously. The techniques of measurement were therefore comparable in the two limbs with no attempt made to separate foot or hand from total limb blood flow. Water temperature in the arm plethysmograph was set to the mean arm skin temperature of one subject while, in the other study, arm bath temperature was adjusted to approximate that of the leg under study. Measurements were performed every two to four minutes throughout the period of heating, alternating the determination from the leg to the arm.

Body temperature measurement. Rectal ( $T_{re}$ ) and three different mean skin temperatures (total body mean skin =  $\bar{T}_{sk}$ , leg mean skin =  $\bar{T}_{skl}$ , and arm mean skin =  $\bar{T}_{ska}$ ) were monitored in each subject. Rectal temperatures were followed at 5-minute intervals throughout the study while surface temperatures were recorded only during the initial one hour equilibration period. In this way, the development



of steady-state  $T_{re}$  and  $T_{sk}$  identified the achievement of thermal equilibrium for each subject prior to resting blood flow measurements. In like fashion,  $T_{ska}$  and  $T_{skl}$  were utilized to set water temperature in the respective plethysmographs to levels which would approximate that of the limb surface under these resting conditions.

Total body and leg mean skin temperatures were calculated as reported previously, while mean arm skin temperature was determined by averaging four surface temperatures - anterior upper arm, posterior upper arm, forearm, and dorsum of hand.

## RESULTS

Thirty minutes of external heating resulted in an average 0.4-0.5°C rise in rectal temperature in control subjects, patients with minimal leg burns, and patients with extensive leg injuries (Table 2). This elevation in central body temperature increased blood flow to the control limbs from a basal level of  $2.93 \pm 0.29$  ml/100 ml·min (mean  $\pm$  S.E.M.) to  $4.57 \pm 0.29$  ml/100 ml·min after heating. This 56% increase in normal leg blood flow was comparable to a 63.2% increase in flow to the essentially uninjured legs of burned patients (from  $3.64 \pm 0.52$  to  $5.94 \pm 0.92$  ml/100 ml·min) over identical periods of external heating. Blood flow to the extensively burned extremities, however, increased by only 9.6% (from  $7.11 \pm 0.78$  to  $7.79 \pm 0.76$  ml/100 ml·min). Generally, in the legs in which reflex vasodilation occurred, this had begun by the end of 10-15 minutes of external heat when the first set of measurements were performed. Flow to these limbs continued to increase and was always higher by the end of 30 minutes of heat loading. There was a general, inverse relationship between size of the leg burn (%LB) and the per cent increase in leg blood flow (%LBF) with external heating (Fig. 1). The limited capacity to vasodilate in the burned limbs was not only apparent in patients with open wounds on their legs (patients 11, 18, and 19) but was also evident in convalescent patients with well healed leg wounds.

In the two patients where simultaneous arm and leg blood flow measurements were monitored, there was a marked increase in blood flow to the uninjured arm, while flow to the burned leg remained essentially unchanged (Fig. 2 & 3). This increase in flow to the arm occurred whether the water bath temperature matched that of the predetermined mean arm skin temperature or was elevated in order to approximate the temperature of the skin of the burned leg.

All subjects sweated freely during the process of external heating, but, in the patients, this sweating could only be visualized from the unburned skin.

TABLE 2. Effects of thirty minutes of external heating on rectal temperature and leg blood flow

Leg Surface Subject Temperature (°C)		Rectal Temperature (°C)		Leg Blood Flow (ml/100 ml·min)*	
		Before	After	Before	After
<u>Controls</u>					
1	34.0	36.6	37.0	2.51 ± 0.09	4.48 ± 0.16
2	34.0	36.7	37.0	4.06 ± 0.18	5.42 ± 0.12
3	33.5	36.7	36.9	2.54 ± 0.10	3.89 ± 0.29
4	33.8	36.7	37.1	2.64 ± 0.16	4.33 ± 0.09
5	33.6	37.0	37.3	2.88 ± 0.22	4.74 ± 0.48
Mean	33.8	36.7	37.1	2.93 ± 0.29	4.57 ± 0.25**
<u>Small Leg Burns</u>					
6	35.3	38.2	38.9	5.04 ± 0.23	7.86 ± 0.42
7	33.6	37.3	37.5	2.75 ± 0.17	4.38 ± 0.19
8	35.7	38.3	38.9	2.88 ± 0.26	4.67 ± 0.09
9	34.4	38.4	38.8	2.79 ± 0.09	4.31 ± 0.30
10	35.1	37.6	38.2	4.76 ± 0.06	8.47 ± 0.56
Mean	34.8	38.0	38.5	3.64 ± 0.52	5.94 ± 0.91***
<u>Large Leg Burns</u>					
11	34.2	37.3	37.4	5.21 ± 0.27	5.57 ± 0.09
12	34.9	37.0	37.6	4.70 ± 0.26	6.41 ± 0.45
13	35.5	37.3	37.6	7.12 ± 0.16	7.18 ± 0.16
14	35.6	37.3	37.6	7.16 ± 0.52	7.61 ± 0.01
15	35.8	37.0	37.3	5.09 ± 0.18	4.88 ± 0.62
16	34.0	37.3	37.6	7.69 ± 0.78	6.15 ± 0.25
17	35.1	36.7	37.5	4.81 ± 0.08	7.69 ± 0.30
18	35.8	37.2	38.1	12.21 ± 0.12	12.68 ± 0.45
18a	35.7	37.2	37.6	10.29 ± 0.37	10.75 ± 0.50
19	36.3	38.7	39.1	6.82 ± 0.46	8.98 ± 0.25
Mean	35.3	37.3	37.7	7.11 ± 0.78	7.79 ± 0.76

\* Mean ± S.E.M.; \*\* p<0.001; \*\*\* p<0.01

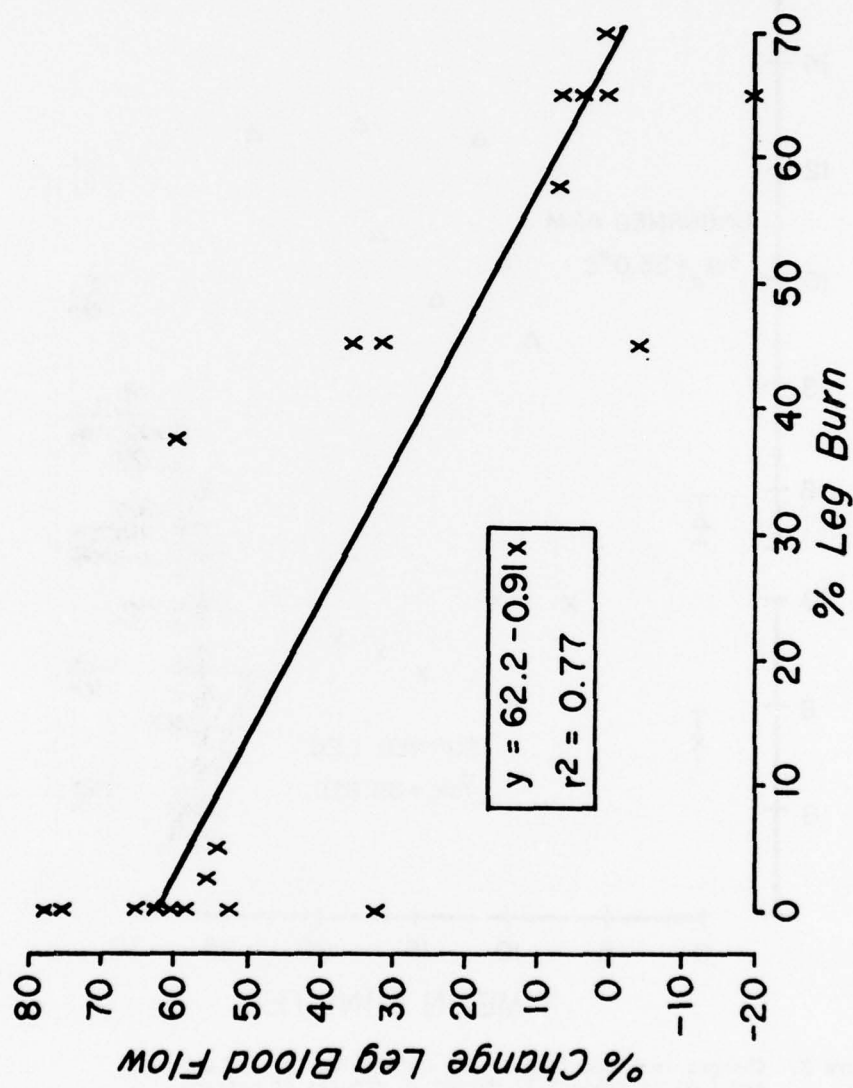


Figure 1. The increase in leg blood flow following 30 minutes of reflex heating decreases with the size of injury on that particular leg.

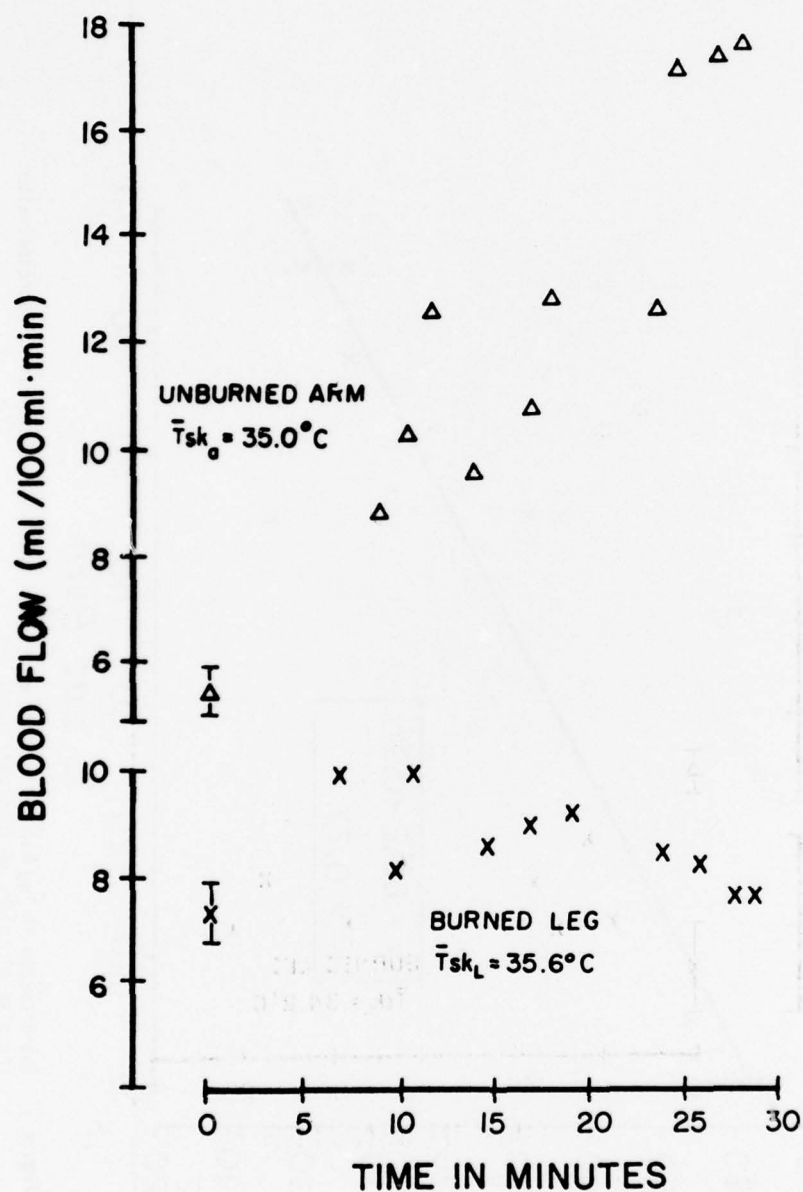


Figure 2. Changes in blood flow to the burned leg (x) and unburned arm ( $\Delta$ ) of subject 11 during 30 minutes of external heating. Surface temperature of each limb was maintained at the predetermined mean skin temperature for that particular extremity. Limb blood flow at time 0 represents the mean  $\pm$  S.E.M. of 4-6 measurements taken just prior to heating.



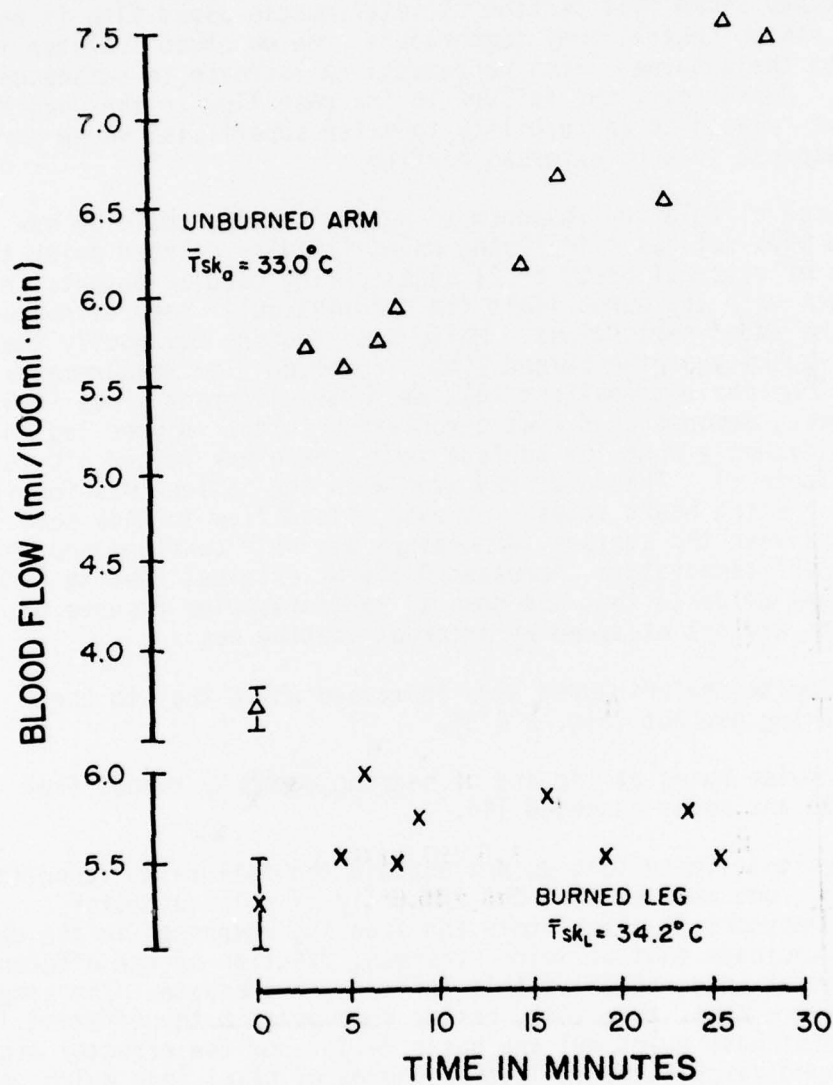


Figure 3. Changes in blood flow to the burned leg (x) and unburned arm ( $\Delta$ ) of subject 14 during 30 minutes of external heating. Surface temperature for both limbs was maintained at a level comparable to that of the burned leg. Leg blood flow at time 0 represents the mean  $\pm$  S.E.M. of 4-6 measurements taken just prior to heating.

## DISCUSSION

This study clearly demonstrates impaired reflex vasodilation in injured limbs which persists for at least 3-4 months postinjury. Since earlier work has shown that resting skeletal muscle blood flow is unaffected by rising central body temperature, the observed increase in blood flow to the unburned limbs represents an increase in cutaneous circulation. Conversely, the failure to increase flow in the burned limbs must be related to an inability to alter superficial wound perfusion in response to such external heating.

The reduced circulatory response to reflex heating could be explained on a physical basis if 1) the wound is fully dilated prior to the addition of external heat, or 2) high resting cardiac outputs in these patients with leg burns limit the cardiovascular reserve needed to support the added heat stress. While both factors may modify the vasodilator capacity of the burned limb, leg blood flow measurements performed on one patient (patient 15), at three different times in his hospital course, demonstrated that circulation to the injured leg increased significantly when leg surface temperature was raised 5°C for 30 minutes (Table 3). This occurred even when the patient was febrile and had high resting heart rates. However, blood flow to this same leg did not change when the surface temperature was held constant and the patient's rectal temperature increased 0.3°C by external heating (Table 2). Additional evidence that the general cardiovascular reserve of these patients was not exceeded by external heating was:

- 1) Blood flow to the uninjured arms increased while that to the burned leg did not (Fig. 2 & 3).
- 2) Maximum pulse rates at the end of heating commonly ranged from 120-130 and never exceeded 144.

Since physical limitations do not explain the failure to vasodilate the burn wound, one must examine the integrity of this vasomotor reflex arc. Appropriate circulatory and sweating responses in the uninjured skin indicate that stimulus strength, function of the afferent limb, and central integration of this reflex were adequate. The site of reflex failure must, therefore, reside somewhere in the efferent limb. Previous studies have ruled out any basic failure of the effector organ, since burn wound vasculature exhibits a degree of basal tone which can be manipulated by direct changes in temperature (Table 3). Consequently, the loss of reflex vasomotor control must indicate that the wound is "functionally" denervated. This could result from 1) an actual physical disruption of sympathetic nerves at the time of injury and/or 2) changes in the local chemical environment which affect wound neuromuscular transmission of the innervated vessels.

TABLE 3. Changes in rectal temperature, leg blood flow and heart rate  
with a 5°C increase in leg surface temperature for 30 minutes

Postburn Day	Rectal Temperature (°C)		Leg Blood Flow* (ml/100 ml·min)		Heart Rate	
	Before	After	Before	After	Before	After
7	38.8	38.8	5.88 ± 0.20	7.90 ± 0.24	110	134
14	37.5	37.8	6.24 ± 0.16	9.32 ± 0.27	110	120
50	37.1	37.4	4.65 ± 0.33	7.91 ± 0.38	84	98

\*Mean ± S.E.M.

Tissue inflammation, whether it be a result of injury or the invasion of microorganisms, is characterized by a local increase in blood flow to the affected site and a secondary spread of this vasodilation, referred to as the arterial flair. These changes in the microcirculation are mediated both by local chemical factors released during injury (i.e., prostaglandins, histamine, serotonin) and various humoral factors introduced via the blood stream - the principle vasoactive agents in this category being the kinins. Many such chemical factors have been identified in the burn wound. The effects of these inflammatory products on local nervous activity was described by Zweifach, who reported that during inflammation precapillary sphincters became refractory to vasoconstrictor stimuli. He then suggested that this refractoriness may be related to the ability of PGE to suppress adrenergic transmission as demonstrated earlier by Horton. (Since prostaglandins also have direct effects on cutaneous vascular smooth muscle, the exact mechanisms by which they affect neurogenic control of small blood vessels in inflammatory tissue is still unclear.) Alternately, local wound chemistry could cause the chronic release of neurotransmitter from vasodilator nerves and thereby limit the capacity of these nerves to respond to additional extrinsic stimuli. In addition to these various inflammatory products, vessels in the burn wounds may be dilated in areas of low oxygen tension or by the enhanced lactate production and elevated temperatures of the local environment. This combination of inflammatory and metabolic factors creates a local chemical environment which could readily reduce the influence of any sympathetic vasomotor nerves in granulation tissue.

In any form of tissue injury, actual physical disruption of sympathetic efferent nerves would also contribute to a reduction in reflex control of wound blood flow. This physical denervation would not only explain the inability to actively vasodilate the burn wound but may also increase basal flow by releasing the microvasculature from tonic neurogenic vasoconstriction.

The prolonged duration of faulty reflex vasomotor control in the burned limbs is consistent with the concept of actual physical denervation, since several studies have demonstrated that nerve regeneration and vascular reinnervation of granulation tissue involves a considerable period of time. A basic time table for such reinnervation was provided by one animal study, where the utilization of transparent chambers permitted direct visualization of the granulating wound. In this particular model, recognizable nerve fibers and active arteriolar contractions were observed on the fringes of the wound as early as 3-4 weeks postinjury. The rate of nerve growth decreased with time, however, and, in some instances, ceased before many newly formed vessels were innervated. In some animals, arterioles were 3.5-7.5 months old before definite active contractions were observed. Others, who have studied the general sensory innervation of skin grafts, have commented



on the slowness of cutaneous nerve regeneration. They concluded that the degree of reinnervation depended on the availability of neurolemmal pathways for the ingrowing nerves. Such pathways were least accessible in split-thickness grafts, which resulted in greater scarring. In the current study, five patients with leg burns (patients 12, 13, 14, 18, 19) had this type of graft on the leg under study.

The relative significance of local chemical factors and primary nerve damage on reflex control of wound blood flow depends both on the extent of actual trauma and the degree of wound repair. Inflammatory and metabolic influences should gradually subside as the wound heals and assumes a character more like that of normal skin. Likewise, nerve regeneration develops slowly and reaches a level of vascular reinnervation ultimately determined by the developing scar.

#### SUMMARY

The data support the concept that burn wound neovasculature is "functionally" denervated. Depending on the extent of trauma and degree of repair, this denervation may include both an actual physical disruption of vasomotor efferent nerves and chemical alterations of neuromuscular transmission in those vessels which retain their innervation. Regardless of the precise mechanism involved, such denervation would 1) elevate basal wound blood flow by releasing the neovasculature from tonic neurogenic vasoconstriction, and 2) prevent active vasodilation (and sweating) in the wound in response to an additional heat stress. This loss of neural control allows local environmental factors to exert a greater influence on wound blood flow. Consequently, the control of wound circulation becomes less like that of normal skin and more like that of other critical tissues (heart, brain, working skeletal muscle), the blood flows of which vary as a function of local metabolic conditions rather than as part of integrated total body thermoregulatory or baroreceptor reflexes.

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ANNUAL PROGRESS REPORT

PROJECT NO. 3S1611102BS05-00, MILITARY BURN RESEARCH

REPORT TITLE: THE STUDY OF METABOLISM AND NUTRITIONAL EFFECTS  
OF BURN INJURY IN SOLDIERS --STUDIES OF DISTURBANCE  
OF PROTEIN TURNOVER IN BURNED TROOPS - USE OF AN  
ANIMAL MODEL

US ARMY INSTITUTE OF SURGICAL RESEARCH  
BROOKE ARMY MEDICAL CENTER  
FORT SAM HOUSTON, TEXAS 78234

1 October 1976 - 30 September 1977

Investigators:

Wanda L. Brown, M.S.  
Eleanor G. Bowler, Ph.M.  
Arthur D. Mason, Jr., M.D.

Reports Control Symbol MEDDH-288(R1)

Unclassified



## ABSTRACT

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US Army Institute of Surgical Research, Brooke Army Medical Center, Fort  
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Groups of rats with a 20% body surface scald burn, or an equivalent sham burn, were treated one hour postburn with a subcutaneous injection into the wound area of 1 ml of hyaluronidase in saline (150 N.F. units) or of 1 ml of 0.15 M saline. Other rats of each group were untreated. All rats were housed in individual cages and permitted free access to food and water but were given no further treatment.

At 6, 24, and 48 hours postburn rats from each group were anesthetized with methoxyflurane. The entire burn or sham wound was excised and was immediately weighed. The whole tissue was dried to constant weight and the water content was determined by difference. Plasma volumes of the burned rats were determined by isotope dilution after injection of  $^{131}\text{I}$ -labeled albumin.

Sham Burns - There were no significant differences between the values in the three treatment groups of sham burned rats (Table 1). Plasma volumes (not shown) determined in other rats were within normal limits under these conditions.

Burns - The results for the untreated and the saline treated burned rats showed only one difference -- a small, but statistically significant, increase in per cent water in the saline treated rats at 6 hours postburn (Table 2).

The water content of the burn wound was similar for all treatment groups at 6 hours postburn. At 24 and 48 hours postburn the water content of the hyaluronidase treated burn wounds was significantly less than that in the other groups.

Table 1. "Eschar" of Sham 20% Body Surface Burn Rats

Time Postburn		Treatment Group			Comparisons ANOV p =	
		Untreated (U)	Saline (S)	Hyaluronidase (HYAL)	U vs S	(U+S) vs (HYAL)
Wet Weight grams	6 hr	8.4803*	8.7530	9.1422	NS	NS
	24 hr	5.1754 - 11.7851	5.4481 - 12.0578	5.8374 - 12.4471	NS	NS
	48 hr	8.5780 7.7445 - 9.4114	7.7599 5.8234 - 9.6963	7.8833 5.9468 - 9.8197	NS	NS
Dry Weight gram	6 hr	2.6942	2.7323	2.7564	NS	NS
	24 hr	1.9124 - 3.4761	1.9505 - 3.5142	1.9764 - 3.5382	NS	NS
	48 hr	2.8836 2.6175 - 3.1496	2.6320 2.0138 - 3.2501	2.5776 1.9594 - 3.1958	NS	NS
Gram Water	6 hr	5.7860	6.0206	6.3859	NS	NS
	24 hr	3.0957 - 8.4763	3.3303 - 8.7109	3.6956 - 9.0761	NS	NS
	48 hr	5.6755 5.0906 - 6.2605	5.1279 3.7687 - 6.4871	5.3057 3.9465 - 6.6648	NS	NS
% Water	6 hr	5.2301	5.0129	5.2619	NS	NS
	24 hr	3.8972 - 6.5629	3.3457 - 6.6801	3.9291 - 6.5948	NS	NS
	48 hr	68.21 61.72 - 74.70	68.76 62.27 - 75.25	69.80 63.31 - 76.29	NS	NS
	24 hr	66.32 65.44 - 67.20	66.07 64.02 - 68.12	67.18 65.13 - 69.23	NS	NS
	48 hr	65.43 63.25 - 67.43	65.77 63.16 - 68.38	66.26 64.17 - 68.35	NS	NS

\* Means and 95% confidence intervals of the means.

Table 2. Eschar of Rats with 20% Body Surface Burn

Time Postburn	Treatment Group	Comparisons ANOV p =		
		U vs S	(U+S) vs (HYAL)	
Wet Weight grams	Untreated (U)	Saline (S)	Hyaluronidase (HYAL)	
6 hr	15.6710*	15.7609	14.8944	NS
	13.3682 - 17.9738	13.4581 - 18.0637	12.5916 - 17.1971	NS
	18.7327	18.4336	14.8588	<0.001
24 hr	17.6064 - 19.8590	16.7178 - 20.1493	13.2003 - 16.5173	NS
	17.7600	18.2410	16.2892	<0.05
48 hr	15.9639 - 19.5561	16.2155 - 20.2664	14.3885 - 18.1898	NS
	3.9177	3.7579	3.7513	NS
Dry Weight grams	Untreated (U)	Saline (S)	Hyaluronidase (HYAL)	
6 hr	3.2883 - 4.5472	3.1285 - 4.3874	3.1219 - 4.3808	NS
	4.2809	4.1682	3.7896	<0.025
	3.9798 - 4.5819	3.7097 - 4.6268	3.3553 - 4.2418	NS
24 hr	4.3538	4.5891	4.4272	NS
	3.7557 - 4.9519	3.9146 - 5.2636	3.7943 - 5.0602	NS
Gram Water	Untreated (U)	Saline (S)	Hyaluronidase (HYAL)	
6 hr	11.7533	12.0030	11.1413	NS
	10.0454 - 13.4611	10.2951 - 13.7108	9.4365 - 12.8522	NS
	14.4517	14.2654	11.0460	<0.001
24 hr	13.5982 - 15.3053	12.9652 - 15.5656	9.7892 - 12.3028	NS
	13.4062	13.6529	11.8544	<0.01
48 hr	12.1300 - 14.6824	12.2137 - 15.0921	10.5039 - 13.2049	NS
	75.01	76.17	74.92	<0.05
% Water	Untreated (U)	Saline (S)	Hyaluronidase (HYAL)	
6 hr	73.91 - 76.11	75.07 - 77.27	73.82 - 76.02	NS
	77.20	77.40	74.45	<0.001
	76.55 - 77.85	76.41 - 78.39	73.49 - 75.40	NS
24 hr	75.52	74.92	72.90	<0.001
	74.04 - 76.99	73.25 - 76.58	71.34 - 74.47	NS
Plasma Volume ml/100 gram	Untreated (U)	Saline (S)	Hyaluronidase (HYAL)	
6 hr	2.85	2.61	3.09	NS
	1.95 - 3.74	1.71 - 3.50	2.20 - 3.99	NS
	3.87	3.99	4.19	<0.05
24 hr	3.61 - 4.12	3.61 - 4.38	3.85 - 4.52	NS
	4.50	4.50	4.61	NS
48 hr	4.06 - 4.94	4.18 - 4.83	4.28 - 4.93	NS

\* Means and confidence intervals of the means.

The water content of the burned wound was significantly higher than that of the sham wound. At 6 hours postburn the burn wounds of the untreated and saline treated rats contained 6.3 gm, and the hyaluronidase treated rats 5.6 gm, more water than did the sham wound. At 24 and 48 hours postburn respectively, the excess water was 8.8 and 7.9 gm for the untreated and saline treated groups, and 5.5 gm and 6.3 gm for the hyaluronidase treated group of burned rats. Even so, the plasma volumes of the burned rats had returned to normal at 24 hours and were slightly greater than normal at 48 hours postburn. Dry weight of all of the burned wounds was greater than that of the sham wound.

We are now measuring the albumin content of the burned rats using these same models to determine whether albumin accumulation in the burn wound is also decreased by hyaluronidase treatment.

Burn Injury  
Protein Metabolism



ANNUAL PROGRESS REPORT

PROJECT NO. 3S1611102BS05-00, MILITARY BURN RESEARCH

REPORT TITLE: The Study of Metabolism and Nutritional Effects of Burn  
Injury in Soldiers (The Development of a Goat Model  
For The Study of Wound Blood Flow)

US ARMY INSTITUTE OF SURGICAL RESEARCH  
BROOKE ARMY MEDICAL CENTER  
FORT SAM HOUSTON, TEXAS 78234

1 October 1976 - 30 September 1977

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Reports Control Symbol MEDDH-288(R1)

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# ABSTRACT

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US Army Institute of Surgical Research, Brooke Army Medical Center, Fort Sam Houston, Texas 78234

Period covered in this report: 1 October 1976 - 30 September 1977

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Reports Control Symbol MEDDH-288(R1)

Peripheral blood flow studies in burn patients have identified numerous questions related to the control of burn wound blood flow. Since most of these can be best answered in an animal model, we propose to evaluate the effect of a 50 per cent, full-thickness leg burn on extremity blood flow in the goat.

Eight to ten goats, weighing approximately 20-40 kg, will be used. Doppler probes will be utilized to measure leg blood flow. They will be placed on the external iliac arteries bilaterally. After 10 days, when the probe-vessel relationship is considered stabilized, leg blood flow measurements will begin, and will be repeated three times weekly in both the awake and lightly anesthetized animals.

After sufficient baseline studies, the animal will be placed under deep anesthesia and the skin of one hind limb will be excised to fascia from the groin to two-three inches proximal to the ankle joint. The wound will then be placed in compression dressings and the animal observed during recovery. The effect of this injury on limb blood flow will be followed for two-three weeks postinjury. Dressings will be changed daily.

After two-three weeks of observation, each probe will be calibrated and the animal sacrificed. Serial biopsies of the wound will be taken weekly under general anesthesia.

These animals will be housed in the dog runs and weighed prior to each experiment. Any additional care required will be provided as needed in consultation with staff veterinarian.

This recently approved study is pending and will proceed as soon as animals are obtained.

Wound blood flow

ANNUAL PROGRESS REPORT

PROJECT NO. 3S1611102BS05-00, MILITARY BURN RESEARCH

REPORT TITLE: The Study of Metabolism and Nutritional Effects  
of Burn Injury in Soldiers (Muscle Blood Flow  
Following Thermal Injury)

US ARMY INSTITUTE OF SURGICAL RESEARCH  
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ABSTRACT

PROJECT NO. 3S1611102BS05-00, MILITARY BURN RESEARCH

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Total limb blood flow is normal in uninjured limbs of burned patients but rises in a curvilinear manner with the extent of limb injury. While this strongly suggests wound directed peripheral blood flow, changes in muscle blood flow with thermal injury is unknown and may contribute to increased perfusion of injured limbs. Resting skeletal muscle blood flow was measured by  $^{133}\text{Xe}$  clearance of the lower leg(s) of 10 burn patients (mean burn size = 42.5%-82% total body surface) and five normals. While the size of leg burn ranged from 0-77.5% of the leg surface, muscle perfusion in these limbs was essentially normal:  $3.52 \pm 0.26$  ml/100 g muscle per minute (mean  $\pm$  S.E.M.) vs.  $3.29 \pm 0.24$  in controls. Muscle blood flow was therefore unaffected by the location or extent of thermal injury or the febrile state of the patient (mean rectal temperature =  $38.9^\circ\text{C}$ ). Normal levels of muscle blood flow in injured legs, where total flow is elevated, confirms the original hypothesis suggesting that most, if not all, of the increased peripheral blood flow following thermal injury is directed to the surface wound.

Peripheral blood flow  
Trauma

## MUSCLE BLOOD FLOW FOLLOWING THERMAL INJURY

Peripheral blood flow is markedly increased during the hyperdynamic phase of thermal injury. This has been adequately established both indirectly (4,9) and by actual peripheral blood flow measurements (1). In the latter case, total leg blood flow, as measured by venous occlusion plethysmography, was essentially normal in uninjured limbs of burned patients but rose in a curvilinear fashion with the extent of local leg burn. While this strongly suggests wound directed peripheral blood flow, this conclusion, based on such total limb blood flow data, must be confirmed by insuring that there are no underlying changes in muscle blood flow in burned limbs. This study was designed to measure muscle blood flow in the legs of burned patients and relate this segment of total limb perfusion to the extent of total body injury, size of burn on that leg, and central body temperature of the patient.

### MATERIAL AND METHODS

#### Subjects

Muscle blood flow was determined in 10 burn patients (mean burn size = 42.5% total body surface, range 25.5-82%) and five normal controls. Since the presence of a constrictive eschar or systemic "sepsis" have been shown to have a marked effect on muscle perfusion (3,6), all patients were studied 6-28 days postinjury when neither complication was evident clinically. Patients were free of any pre-existing disease prior to injury; normotensive and hemodynamically stable, and in a normal state of hydration with an hematocrit above 33 and without abnormalities in serum electrolyte concentration, osmolality, or pH. Burn wounds were treated by the standard open method utilizing either topical application of silver sulfadiazene cream (Silvadene<sup>R</sup>) or 11% mafenide acetate (Sulfamylon<sup>R</sup>).

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1. Aulick LH, Wilmore DW, Mason AD Jr, Pruitt BA Jr: Influence of the burn wound on peripheral circulation in thermally injured patients. *Am J Physiol* 233(4):H520-H526, 1977.

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## Methods

All subjects were confined to bed for a minimum of one hour prior to muscle blood flow measurements. The actual studies took place in the Nuclear Medicine Clinic of the hospital where the ambient temperature was 25-27°C. Since this was slightly below thermal neutrality for resting burned patients (10), they were covered with light cotton blankets. All subjects rested supine throughout the 20-30 minute study. Most patients slept quietly during the actual test, and a few had to be disqualified due to involuntary leg and/or foot movements while asleep.

## Muscle Blood Determination

Radioactive xenon gas ( $^{133}\text{Xe}$ ) was dissolved in sterile 0.9% NaCl solution to a concentration of 0.5-1.0  $\mu\text{C}/\text{ml}$ , and 0.1-0.2 ml of this solution was injected 1-2 cm into the tibialis anterior muscle through a 25 gauge hypodermic needle. The disappearance of  $^{133}\text{Xe}$  was monitored for 20-30 minutes postinjection by a collimated scintillation probe placed directly over the injection site. Muscle blood flow (MBF) in ml/100 g muscle tissue per minute was calculated from the tangent to the logarithmic curve of  $^{133}\text{Xe}$  washout as described previously by Lassen et al (5). Whenever feasible, simultaneous measurements were performed on both legs.

## RESULTS AND DISCUSSION

Resting skeletal muscle blood flow was essentially normal in this group of 10 burn patients:  $3.52 \pm 0.26$  (mean + S.E.M.) as compared to  $3.29 \pm 0.24$  in controls (Table 1). Therefore, unlike total limb perfusion, which varies with the extent of local injury (1), muscle blood flow was unrelated to the size of leg burn. The absence of a local burn effect on muscle perfusion was particularly evident from simultaneous measurements in patients (Numbers 6, 9, and 12) with asymmetrical leg burns. These results confirm the interpretations of previous studies (1) which suggested that most of the increased peripheral blood flow following thermal injury was directed to the surface wound.

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10. Wilmore DW, Orcutt TW, Mason AD Jr, Pruitt BA Jr: Alterations in hypothalamic function following thermal injury. *J Trauma* 15:697, 1975.

5. Lassen NA, Lindbjerg, Munck O: Measurement of blood flow through skeletal muscle by intramuscular injection of Xenon-133. *Lancet* 1:686, 1964.

1. Aulick LH, Wilmore DW, Mason AD Jr, Pruitt BA Jr: Influence of the burn wound on peripheral circulation in thermally injured patients. *Am J Physiol* 233(4):H520-H526, 1977.

TABLE 1

SUBJECT*	AGE (Years)	WEIGHT (kg)	PBD	% TBS	% LB	MBF (ml/100 g·min)	T <sub>re</sub> (°C)
<u>Controls</u>							
1a	36	79.5				2.76	37.2
b						2.89	37.2
c						2.17	37.2
d						2.87	37.2
2a	25	75.0				4.76	37.0
b						3.23	37.6
c						4.29	37.6
3	30	81.8				3.16	36.8
4a	26	75.0				3.52	37.3
b						3.99	37.3
5a	29	65.9				2.04	36.9
b						3.77	36.9
Mean	29	75.4				3.29	37.2
<u>Patients</u>							
6a	47	82	13	25.5	7.5	2.42	37.8
b					70	2.50	
7	46	108	10	27	0	3.25	37.9
8	22	52.7	8	33	10	2.60	38.7
9a	19	72.3	12	37	15	5.94	39.0
b					20	4.89	
10a	34	86	28	38	15	2.51	39.4
b					15	4.65	
11	48	73.6	11	40	62.5	3.20	38.1
12a	18	72.7	8	40	10	2.94	38.0
b					25	2.84	
13	27	72.6	6	49.5	50	3.94	38.3
14	22	65.9	20	51.5	40	4.10	39.2
15a	19	58.6	13	82	77.5	3.28	39.0
b					77.5	3.70	
Mean	30	74.4	13	42.5	33	3.52	38.9

\*1cd, 2bc, 4ab, 5ab, 6ab, 9ab, 10ab, 12ab, and 15ab are simultaneous measurements in both legs.



Since muscle blood flow is unaffected by the location of the surface burn, does it vary with either systemic or local metabolic responses to injury? Previous work has shown that systemic changes in total body metabolism, circulation, and temperatures are generally related to the size of total body surface injury (8,11). In this group of 10 patients, however, variations in muscle blood flow were unexplained by differences in either total body burn size or central body temperature. Substrate turnover studies across burned and unburned limbs (11) have suggested that resting skeletal muscle oxygen consumption increases in proportion to changes in total body aerobic demands (presumably for the oxidation of fat) and are unrelated to variations in limb perfusion. This data, combined with the present findings on muscle blood flow, suggests that, unlike working skeletal muscle, the reported rise in resting muscle oxygen uptake in burn patients occurs via increased oxygen extraction rather than any change in rate of delivery. Another important local metabolic event associated with burn injury and apparently having no effect on muscle perfusion is the marked increase in proteolysis and peripheral release of amino acids (2).

These peripheral blood flow measurements in burn patients and others in normals make it possible to characterize the shift in limb blood flow following thermal injury (Fig. 1). Stolwilk (7) has partitioned resting leg blood flow as follows: 29% to muscle, 46% to skin, and 25% to the remainder. Earlier, we reported a slight but insignificant increase in blood flow to the unburned legs of burned patients (1). Assuming little or no change in either muscle, fat,

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11. Wilmore DW, Aulick LH, Mason AD Jr, Pruitt BA Jr: Influence of the burn wound on local and systemic responses to injury. *Ann Surg* 186:444-458, 1977.

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1. Aulick LH, Wilmore DW, Mason AD Jr, Pruitt BA Jr: Influence of the burn wound on peripheral circulation in thermally injured patients. *Am J Physiol* 233(4):H520-H526, 1977.

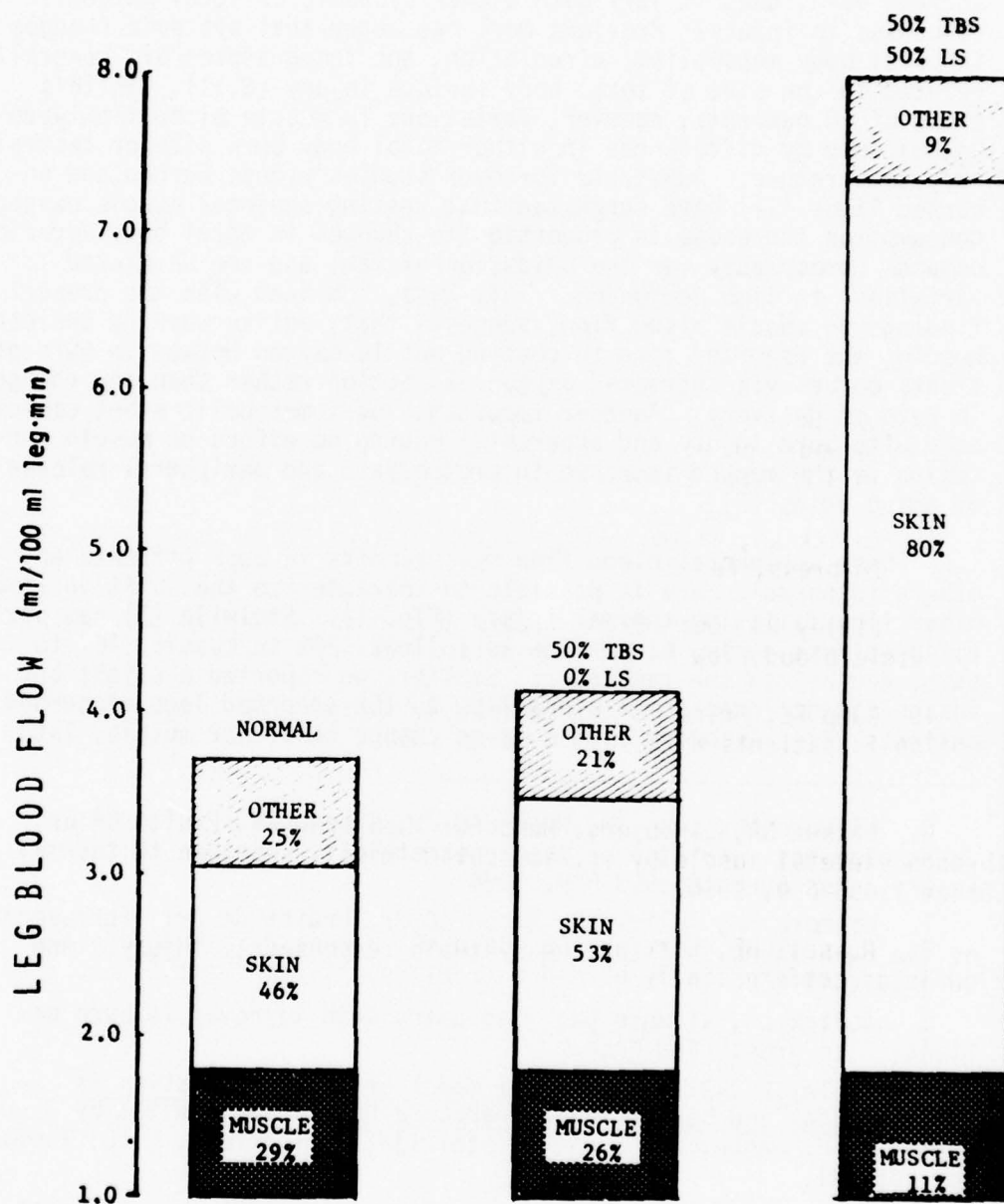


Figure 1

or bone perfusion, blood flow to the skin of an unburned leg in a typical patient with a 50% total body surface burn wound increases by no more than 7% above normal. Since this typical patient is febrile, having a rectal temperature between 38-39°C, the limited increase in superficial blood flow to uninjured skin reflects appropriate cutaneous vasoconstriction for the generation and maintenance of a fever. If this same patient had a burn wound which covered 50% of his leg, limb blood flow would approach 8 ml/100 ml of leg volume per minute (1). Eighty per cent of this total flow would be directed to the leg surface, with the vast majority of this superficial flow going to the burn wound.

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5. Lassen NA, Lindbjerg, Munck O: Measurement of blood flow through skeletal muscle by intramuscular injection of Xenon-133. *Lancet* 1:686-689, 1964.
6. Russell HE, Hartford CE, Boyd WC, Barnes RW: Muscle blood flow in circumferentially burned extremities. *Surg Forum* 26:71, 1975.
7. Stolwijk JAJ: Mathematical Model of Thermoregulation in Physiological and Behavioral Temperature Regulation, edited by J. D. Hardy, A. P. Gagge, and J. A. J. Stolwijk, Springfield, C. C. Thomas, pp. 703-721.
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11. Wilmore DW, Aulick LH, Mason AD Jr, Pruitt BA Jr: Influence of the burn wound on local and systemic responses to injury. Ann Surg 186:444-458, 1977.

#### PRESENTATIONS

Aulick LH: Muscle Blood Flow in Burned Patients. American Physiological Society, Hollywood, Florida, October 1977.

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Aulick LH, Wilmore DW, Mason AD Jr: Muscle blood flow in burn patients. The Physiologist 20:3, 1977.





PROGRESS REPORT

PROJECT NO. 3S1611102BS05-00, MILITARY BURN RESEARCH

REPORT TITLE: THE HEMODYNAMIC RESPONSE TO THERMAL INJURY IN BURNED SOLDIERS. I. SEQUENTIAL HEMODYNAMIC ALTERATIONS IN SEVERE THERMAL INJURY IN THE MILITARY POPULATION -- COLLOID-CRYSTALLOID VERSUS CRYSTALLOID FLUID RESUSCITATION

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# ABSTRACT

PROJECT NO. 3S1611102BS05-00, MILITARY BURN RESEARCH

REPORT TITLE: THE HEMODYNAMIC RESPONSE TO THERMAL INJURY IN BURNED SOLDIERS. I. SEQUENTIAL HEMODYNAMIC ALTERATIONS IN SEVERE THERMAL INJURY IN THE MILITARY POPULATION -- COLLOID-CRYSTALLOID VERSUS CRYSTALLOID FLUID RESUSCITATION

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Direct left ventricular performance during the treatment of postburn shock is not well defined. Prior studies have suggested that crystalloid resuscitation alone will re-establish an adequate cardiac index within 24 hours postburn. Failure to achieve an adequate level is thought to be secondary to a serum myocardial depressant factor. This prospective study evaluated the left ventricular performance in 44 patients during postburn resuscitation. It compared the therapeutic effects of a colloid-crystalloid resuscitation fluid (Group I, n = 22) versus crystalloid fluid alone (Group II, n = 22) in the first 24 hours.

Conclusions: Cardiac index was significantly decreased in the immediate postburn period and remained low in the majority of patients treated with crystalloid fluid alone. Myocardial performance as measured by echocardiographic mean rate of internal fiber shortening was supranormal during this period. Echocardiographic ejection fraction revealed no myocardial depression even in those patients with inadequate cardiac index. These data suggest that the decreased cardiac index often seen in postburn resuscitation is due to the inadequate re-expansion of the vascular space by crystalloid therapy rather than the presence of a serum myocardial depressant factor.

Postburn shock  
Resuscitation fluid

Left ventricular function  
Echocardiography

THE HEMODYNAMIC RESPONSE TO THERMAL INJURY IN BURNED SOLDIERS.  
I. SEQUENTIAL HEMODYNAMIC ALTERATIONS IN SEVERE THERMAL INJURY  
IN THE MILITARY POPULATION -- COLLOID-CRYSTALLOID VERSUS  
CRYSTALLOID FLUID RESUSCITATION

Central hemodynamic changes immediately following severe thermal injury (greater than 40%) have been studied in the experimental animal (1-4) and man (5-7). Hypotension, severe metabolic acidosis, neurological impairment, renal failure, and cardiovascular collapse are manifestations of an immediate reduction of "effective" vascular volume. This circulatory state has been defined as "burn shock" (1,8). The exact pathophysiology is unclear (9), but is apparently due to the inability of central and peripheral cardiovascular compensatory mechanisms to maintain adequate cardiac output for oxygen delivery. Fortunately, this syndrome is rare, because of the increased utilization of aggressive early parenteral volume replacement. Rapid restoration of an "effective" cardiac output has almost eliminated renal failure and cardiovascular collapse as a cause of early death postburn (10). Therefore, the primary therapeutic objective in

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severe thermal injury is the restoration and maintenance of a normal cardiac output without detrimental cardiopulmonary effects.

The composition and rate of infusion of volume replacement have evolved from two different viewpoints. One is that crystalloid solutions (isotonic or hypertonic) alone are sufficient to restore "adequate" cardiac output in the first 24 hours postburn (11-15). The second viewpoint stresses that the addition of a colloid component is more physiologic and more rapidly achieves the desired result (16-20). Scientific documentation in man as to the efficacy of one approach over the others in a prospective manner is lacking, although some preliminary information is available (19).

Schoemaker et al (7) have shown that the hemodynamic alterations in patients resuscitated with a colloid-crystalloid fluid follow a consistent pattern. In the first several hours postburn, the cardiac output is reduced until the patient is rehydrated. The cardiac outputs are then elevated to a supranormal level (usually at 16-24 hours). This is considerably different from the data reported by Baxter's group, using only crystalloid resuscitation (11,12). They suggest that replacement of an "obligatory fluid loss" with isotonic crystalloid fluid more rapidly restores the functional extracellular fluid (ECF) (12). Close scrutiny of Baxter's published curves

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revealed that only patients with small burns (35-40% total body surface burn) achieve an acceptable cardiac index (12). They attribute the failure to achieve an adequate cardiac output to the presence of a circulating serum myocardial depressant factor (MDF). Other studies have identified no greater intravascular retention of colloid-containing fluid than an equal volume of crystalloid fluid (6). Canine studies of Moylan et al (4) also showed that colloid exerted no specific effect on restoration of cardiac output postburn.

This study prospectively compared the hemodynamic patterns post-thermal injury in patients receiving volume resuscitation with a crystalloid solution alone versus a colloid-crystalloid combination. It evaluated the effectiveness of each to restore and maintain circulatory volume. In addition, it utilized direct measurements of intrinsic myocardial function to examine the effect of severe thermal injury and its treatment on left ventricular function.

#### METHODS

Forty-four patients with total body surface burns (TBSB) greater than 30% were studied within the first 16 hours postburn. The study consisted of two phases. In both phases, the patients were allocated to two groups: Group I (n = 22) were those treated with a colloid-crystalloid fluid resuscitation; Group II (n = 22) received only crystalloid volume replacement in the first 24 hours. All patients received colloid solution after 24 hours postburn. All hemodynamic and echocardiographic (ECHO) studies were started when the patient arrived at our Burn Center. The type of volume resuscitation was designated at the first contact with the referring institution.

##### Study Phase 1

In this part of the study, the patients were alternately assigned to Group I (n = 7) or Group II (n = 8). No attempt was made to match them according to age, TBSB, or sex. The volume replacement was controlled only by a minimum criteria for systolic arterial pressure, central venous pressure, and urinary output. No maximum criteria for adjustment of infusion rate were used. Colloid utilized was a commercially available salt-free albumin (SFA). This contained 25 grams of albumin per 100 cc of solution. This was given as a bolus infusion without mixing with a crystalloid solution. Only thermolilution cardiac output measurements were performed in this phase. These were obtained at 2-hour intervals throughout the study period.

##### Study Phase 2

In this phase, patients were assigned to Group I (n = 15) or Group II (n = 14), and matched for age and TBSB. Their volume resuscitation was limited according to several clinical criteria

evaluated on an hourly basis. Their systolic arterial blood pressure was maintained at greater than 100 mm Hg. Urinary output was kept at greater than 30 cc/hr but less than 50 cc/hr. Those patients in Group I received continuous colloid infusion (12.5 grams of SFA per 1,000 cc of Ringer's lactate). Sodium content of the SFA was measured on several occasions (mean value was 135 mEq/L).

All of the patients in Study Phase 2 were evaluated by echocardiography. ECHO measurements of left ventricular function are listed in Table 1. All studies were performed in a standard interspace as described by Popp et al (21). A representative echogram at the point where the left ventricular measurements are taken is depicted in Figure 1. ECHO analysis was performed on a programmable Hewlett-Packard 9830 desk computer used in conjunction with a digitizer, plotter, and tape memory unit. Left ventricular diameter and volume curves obtained from the ECHO measurements are depicted in Figures 2 and 3 respectively. Thermodilution cardiac output measurements were obtained in eight of the 29 patients (Group I, n = 4; Group II, n = 4) in this part of the study. These were then correlated to the cardiac outputs calculated from ECHO.

Table 1. Echocardiographic Measurements of Left Ventricular Function

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1. LV end diastolic dimension (EDD)
  2. LV end systolic dimension (ESD)
  3. LV end diastolic volume (EDV)
  4. LV end systolic volume (ESV)
  5. Stroke volume ( $SV = EDV - ESV$ )
  6. Ejection fraction ( $EDV/SV$ )
  7. Mean rate of internal fiber shortening ( $V_{cf}$ )
  8. ECHO-cardiac output ( $HR \times SV = CO$ )
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Data analysis was performed in three designated resuscitation time periods: initial postburn period (0-12 hours), middle postburn period (12-24 hours), and late postburn period (24-48 hours). Statistical analysis was performed using a Student t-test for unpaired data. Normal values for ECHO indices and cardiac output were used from a normal cath population courtesy of Brooke Army Medical Center Cardiac Catheterization and Noninvasive Laboratories.

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# ECHOLV INTERNAL DIMENSIONS

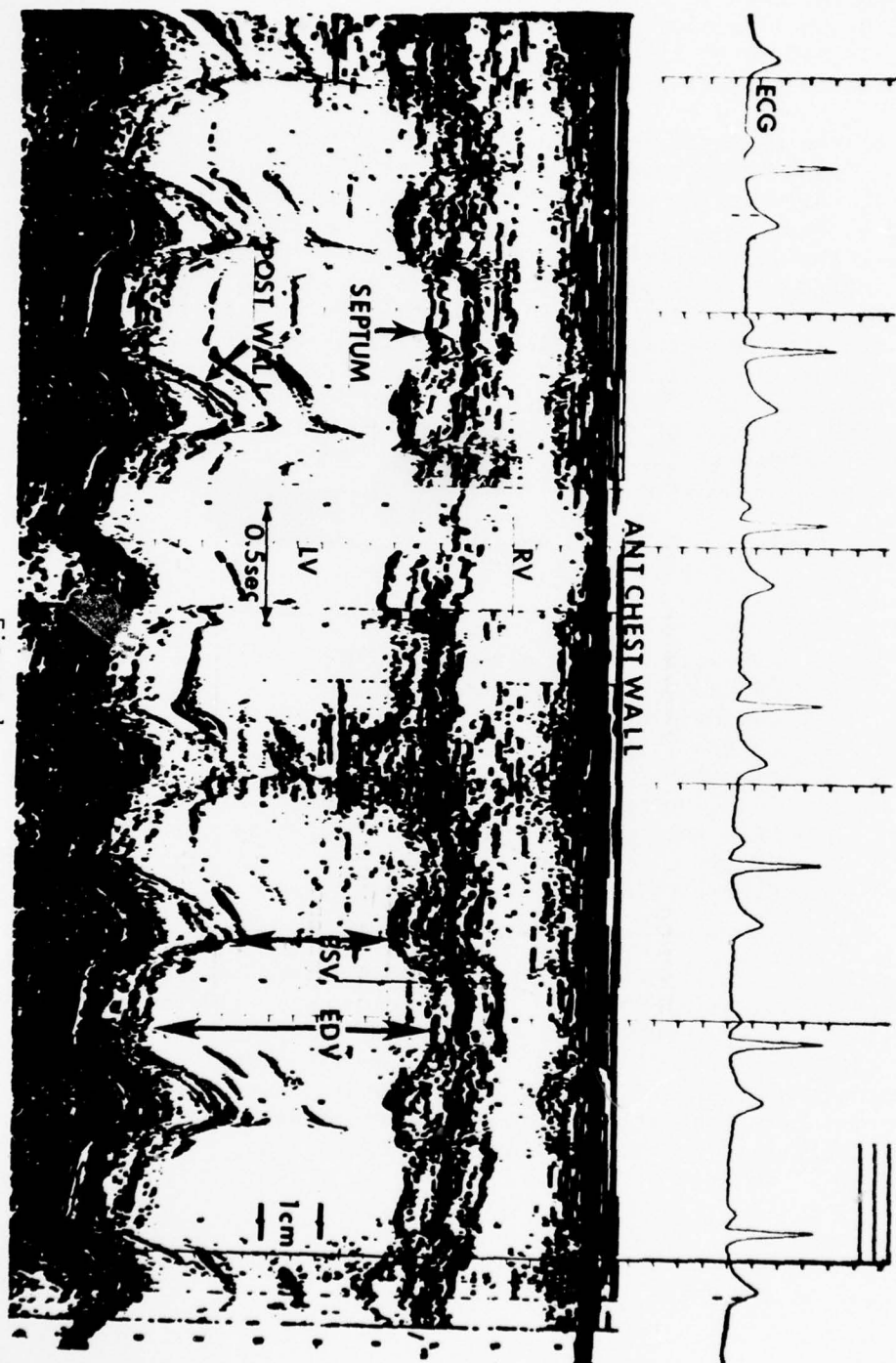


Figure 1



# ECHOCARDIOGRAPHIC LEFT VENTRICULAR DIMENSIONS

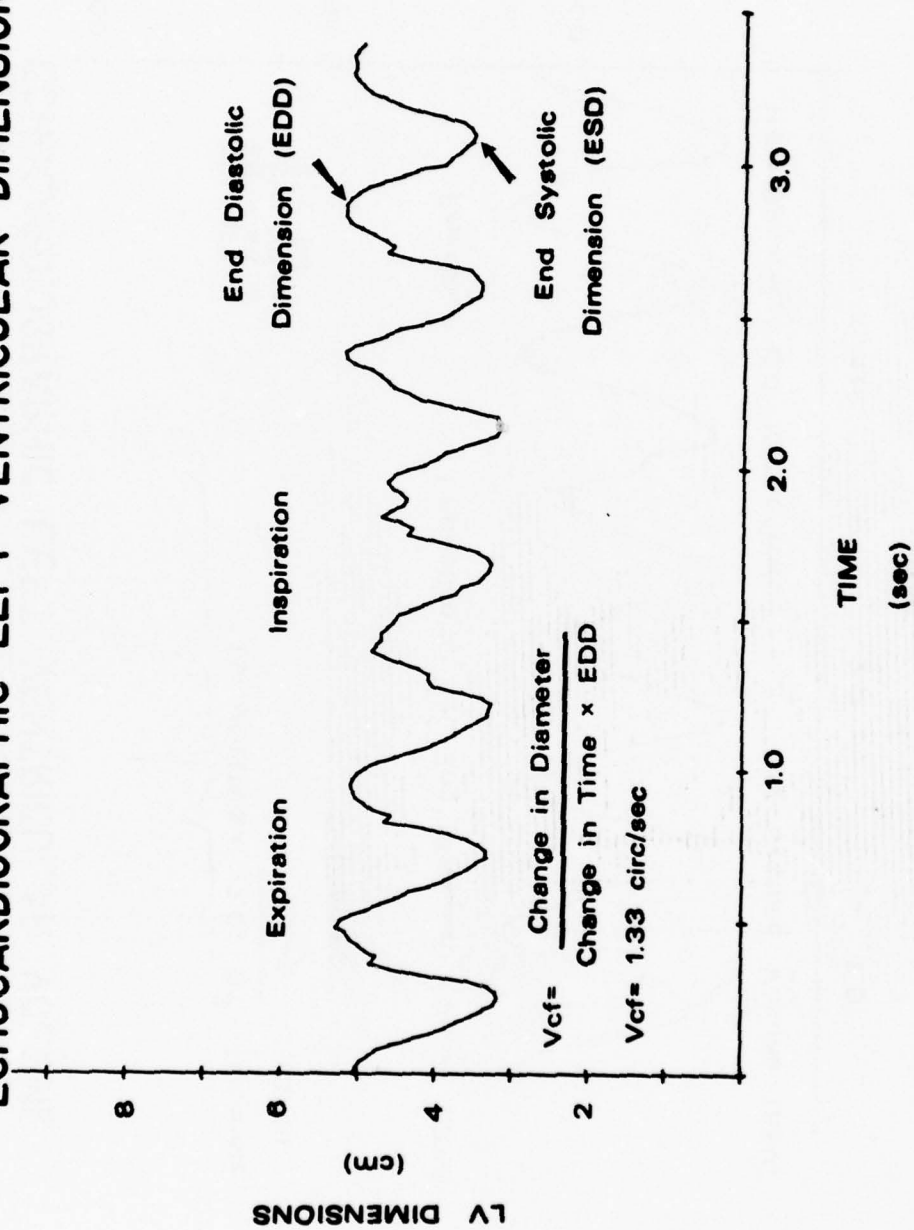


Figure 2

# ECHOCARDIOGRAPHIC LEFT VENTRICULAR VOLUME

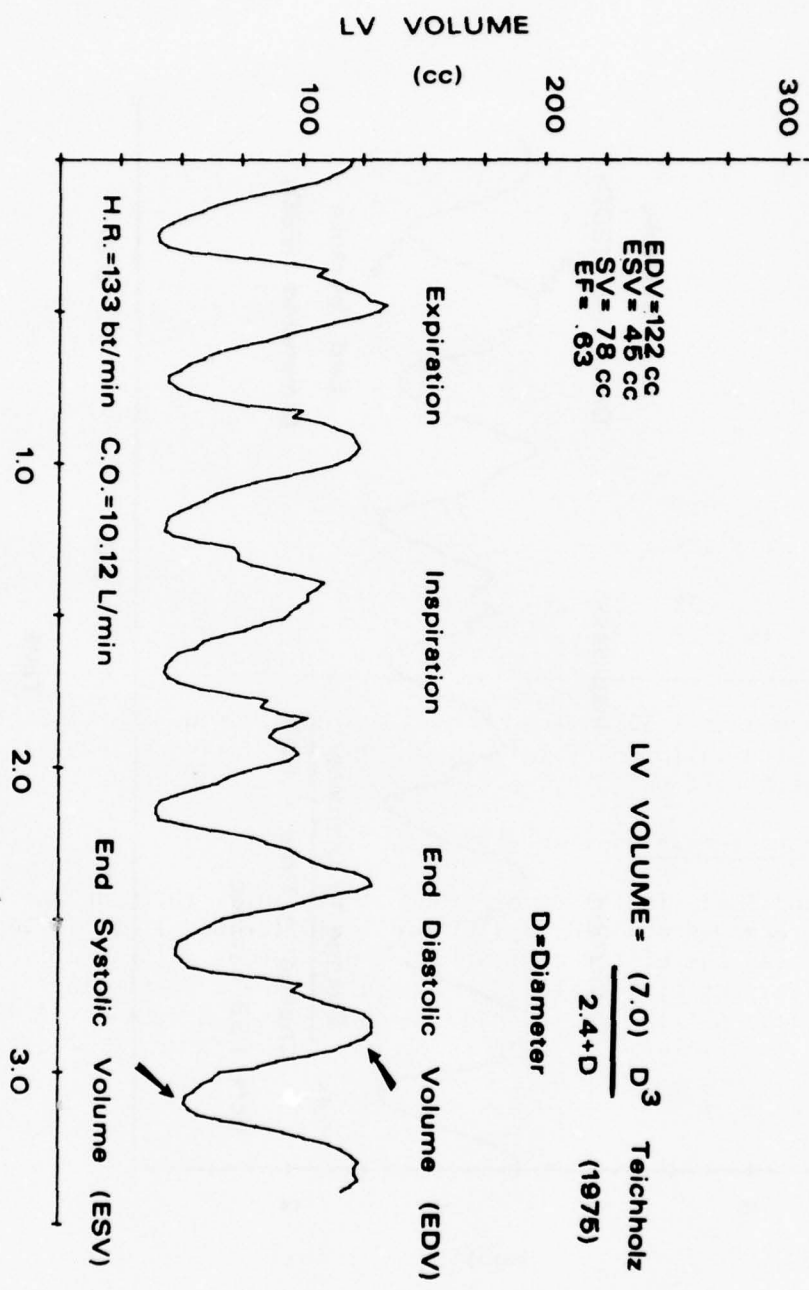


Figure 3

## RESULTS

The patient distribution and the number of individuals in each study phase and group are listed in Table 2. Twenty-two patients were resuscitated with a colloid-crystalloid fluid (Group I) and 22 with a crystalloid solution alone (Group II). Fifteen patients (Group I,  $n = 7$ ; Group II,  $n = 8$ ) were studied with thermodilution measurements only (Study Phase 1). Twenty-nine patients (Group I,  $n = 15$ ; Group II,  $n = 14$ ) were studied with ECHO (Study Phase 2). Eight of the latter (Group I,  $n = 4$ ; Group II,  $n = 4$ ) were also studied with thermodilution cardiac output obtained simultaneously with ECHO cardiac output.

Table 2. Patient Characteristics

Study Phase	Group	n	Age	TBSB	3rd <sup>O</sup>	BSA
1	I	7	$22 \pm 5$	$73 \pm 10$	$29 \pm 15$	$1.87 \pm 0.24$
	II	8	$40 \pm 16^*$	$67 \pm 12$	$32 \pm 23$	$1.89 \pm 0.07$
2	I	15	$27 \pm 10$	$58 \pm 20$	$19 \pm 19$	$1.92 \pm 0.17$
	II	14	$29 \pm 12$	$55 \pm 21$	$44 \pm 29$	$1.92 \pm 0.20$
Total	I	22	$26 \pm 9$	$63 \pm 19$	$23 \pm 18$	$1.90 \pm 0.19$
	II	22	$32 \pm 14$	$59 \pm 19$	$37 \pm 26$	$1.90 \pm 0.16$

Values = mean  $\pm$  1 SD; n = number of subjects; Group I = patients treated with colloid-crystalloid, Group II = patients treated with crystalloid only; \*  $p < 0.05$ , Group II versus Group I

### Patient Characteristics (Table 2)

**Age and Sex:** In the total group of patients, the mean age of those who received colloid-crystalloid fluid (Group I) was 26 years, while the mean age of the crystalloid group (Group II) was 32 years. In the first part of the study, the mean ages were statistically different. These patients were randomized to either Group I or Group II, and the only differences was their age. Neither their clinical course nor autopsy findings were different. In the total group, there was a predominance of males ( $n = 38$  versus 6 females).

**Total Body Surface Burn Percentage:** The mean TBSB was larger in Group I patients but not statistically different (Group I, 63% TBSB versus Group II, 59% TBSB). Estimates of the extent of third degree involvement were higher in Study Phase 2, Group II (44% versus 19%). More patients had larger than 50% TBSB in Study Phase I (14/15 versus 17/29). However, no significant distribution differences

existed between Group I and Group II in either study phase. Approximately 30% (13/44) of the patients had 30-50% TBSB, 50% (22/44) were in the 50-80% range, and 20% (9/44) had greater than 80% TBSB (Table 3).

Table 3. Distribution of Patients on the Basis of Total Body Surface Burn

Study Phase	Group	n	% Total Body Surface Burn		
			30-50	50-80	> 80
1	I	7	0 (0)	5 (71)	2 (29)
	II	8	1 (13)	6 (75)	1 (13)
2	I	15	6 (40)	6 (40)	3 (20)
	II	14	6 (43)	5 (36)	3 (21)
Total	I	22	6 (27)	11 (50)	5 (23)
	II	22	7 (32)	11 (50)	4 (18)

n = number of patients; ( ) = % of total in that group

#### Clinical Course

The average time postburn until entrance into the study was  $10.5 \pm 4.6$  hours (Table 4). This was consistent in both phases.

Table 4. Clinical Course of Patients

Study Phase	Entrance Time Postburn (Hr)	Mortality	Autopsy	Days Postburn to Death
1	$10.6 \pm 4.2$	13/15 (87)	7/13 (53)	$8.3 \pm 5.6$
2	$10.5 \pm 4.9$	15/29 (52)	13/15 (87)	$5.3 \pm 4.8$
Total	$10.5 \pm 4.6$	28/44 (65)	20/28 (71)	$6.6 \pm 5.3$

Values = mean  $\pm$  1 SD; ( ) = % of total in that phase

No patients were entered into the study after 16 hours postburn. The overall mortality was 65%, with a higher percentage in Phase 1. Only four patients died within 72 hours postburn, and all were in Study Phase 2, Group II. The time in days from burn to death was short ( $6.6 \pm 5.3$  days), and reflected the critical condition of these patients. Autopsies were obtained in 71% of the fatalities.



### Volume Resuscitation and Urine Output

The amount and type of volume received in the respective time periods are listed in Tables 5, 6 and 7. Values were calculated on the basis of cc's per kilogram per estimate of TBSB (cc/kg/% burn) over a 24-hour period. In both phases, each group received equivalent amounts of crystalloid volume during each time period.

Table 5. Volume Resuscitation and Urine Output in Study Phase 1

	Group	0-12 Hr	12-24 Hr	Total
Ringer's lactate (cc/kg/% burn)	I	3.92 $\pm$ 0.55	2.53 $\pm$ 0.39*	3.23 $\pm$ 0.36
	II	4.74 $\pm$ 0.50	3.16 $\pm$ 0.57*	3.96 $\pm$ 0.32
Colloid <sup>†</sup> (cc/kg/% burn)	I	0.19 $\pm$ 0.08	0.29 $\pm$ 0.04	0.26 $\pm$ 0.04
Urine output (cc/hr)	I	57 $\pm$ 6	86 $\pm$ 10	72 $\pm$ 6
	II	73 $\pm$ 18	63 $\pm$ 6	68 $\pm$ 9

Values = mean  $\pm$  1 SEM; Group I = patients treated with colloid-crystalloid; Group II = patients treated with crystalloid only; \* p < 0.001 when compared to 0-12 hour time period; <sup>†</sup> Colloid = .25 Gm of albumin per cc of solution

Table 6. Volume Resuscitation and Urine Output in Study Phase 2

	Group	0-12 Hr	12-24 Hr	Total
Ringer's lactate (cc/kg/% burn)	I	4.12 $\pm$ 0.34	2.11 $\pm$ 0.23*	3.12 $\pm$ 0.24
	II	4.70 $\pm$ 0.61	2.46 $\pm$ 0.23*	3.94 $\pm$ 0.60
Colloid <sup>†</sup> (cc/kg/% burn)	I	0.20 $\pm$ 0.05	0.17 $\pm$ 0.03	0.18 $\pm$ 0.03
Urine output (cc/hr)	I	75 $\pm$ 11	56 $\pm$ 8	65 $\pm$ 8
	II	54 $\pm$ 7	49 $\pm$ 7	53 $\pm$ 6

Values = mean  $\pm$  1 SEM; Group I = patients treated with colloid-crystalloid; Group II = patients treated with crystalloid only; \* p < 0.001 when compared to 0-12 hour time period; <sup>†</sup> Colloid = .25 Gm of albumin per cc of solution

Table 7. Volume Resuscitation and Urine Output in Total Patient Population

	Group	0-12 Hr	12-24 Hr	Total
Ringer's lactate (cc/kg/% burn)	I	4.06 $\pm$ 0.29	2.24 $\pm$ 0.20*	3.15 $\pm$ 0.20
	II	4.72 $\pm$ 0.42	2.77 $\pm$ 0.29*	3.94 $\pm$ 0.39
Colloid <sup>†</sup> (cc/kg/% burn)	I	0.20 $\pm$ 0.04	0.21 $\pm$ 0.02	0.21 $\pm$ 0.02
Urine output (cc/hr)	I	69 $\pm$ 7	67 $\pm$ 7	68 $\pm$ 6
	II	61 $\pm$ 8	55 $\pm$ 5	59 $\pm$ 5

Values = mean  $\pm$  1 SEM; Group I = patients treated with colloid-crystalloid; Group II = patients treated with crystalloid only; \* p < 0.001 when compared to 0-12 hour time period; <sup>†</sup> Colloid = .25 Gm of albumin per cc of solution

The amount of crystalloid replacement was decreased in the 12-24 hour period (Table 7, p < 0.001). This represented approximately one-half the volume requirement when compared to the early postburn period. In the total patient population, Group I received Ringer's lactate at approximately 3 cc/kg/% burn in 24 hours, while Group II patients received 4 cc/kg/% burn of crystalloid. The colloid group received an additional .20 cc/kg/% burn in 24 hours as SFA. Urine output was similar in both groups, and did not accurately reflect the overall hemodynamic status of individual patients.

#### Cardiac Index

A total of 297 measurements of cardiac index were obtained (162 during the 0-12 hour period and 135 in the 12-24 hour period). Group I patients had 154 measurements while Group II patients had 143. The distribution of a normal cardiac index (CI) during each time phase is listed as a percentage in Table 8 (CI > 2.6 L/min/m<sup>2</sup>). Only 35% of the CI measurements in the crystalloid group were within normal limits, while 89% of those in the colloid-crystalloid group were normal. The most pronounced difference was during the 12-24 hour period, when only 22% of Group II CI measurements were normal versus 93% in Group I. Every patient resuscitated with the colloid-crystalloid combination achieved and maintained a normal CI during the 12-24 hour period. In contrast, greater than 50% of those in Group II never achieved a normal measurement until given colloid in the 24-48 hour period.

Table 8. Normal Cardiac Index Distribution in Each Time Phase

Study Phase	Group	Time Period (Hr)		Total
		0-12	12-24	
1	I	58	84	78
	II	40	34	35
2	I	86	97	94
	II	42	0	33
Total	I	77	93	89
	II	41	22	35

Values = % of CI measurements taken in that time period

The CI of the two groups is shown in Table 9. Cardiac index was significantly decreased in the early postburn period in both groups.

Table 9. Thermodilution Cardiac Index during Postburn Volume Resuscitation

Study Phase	Group	Time Period (Hr)		
		0-12	12-24	24-48
1	I	2.88 ± 0.22	3.41 ± 0.12*	
	II	2.36 ± 0.16	2.52 ± 0.14†	
2	I	3.18 ± 0.25	3.97 ± 0.22*	
	II	2.59 ± 0.16	2.14 ± 0.12†	
Total	I	3.01 ± 0.17	3.58 ± 0.11*	4.17 ± 0.62§
	II	2.51 ± 0.12	2.41 ± 0.11†	3.74 ± 0.45§

Values = mean ± 1 SEM; \* p < 0.05, 0-12 hr vs 12-24 hr;  
† p < 0.001, Group II vs Group I; § p < 0.05, 24-48 hr vs 0-12 hr; normal CI = 3.6 ± 0.02 L/min/m<sup>2</sup>

No patients were evaluated prior to any therapy, but at the end of 12 hours postburn, those patients resuscitated with a crystalloid solution were abnormal (p < 0.01; normal CI = 3.6 ± 0.2 L/min/m<sup>2</sup>). However, they were not statistically different from the patients treated with a combined colloid-crystalloid fluid (2.51 ± 0.12 versus 3.01 ± 0.17 respectively). In both study phases, there was a marked

difference between Group I and Group II in the 12-24 hour period ( $3.97 \pm 0.22$  versus  $2.14 \pm 0.12$  L/min/m<sup>2</sup>,  $p < 0.001$ ). The CI in the crystalloid group remained abnormal until colloid was added to their therapy at the end of 24 hours. In this time phase (24-48 hours), there was no difference between Group I and Group II.

#### Echocardiographic Measurements

The CI as calculated from ECHO measurements revealed similar differences (Table 10). The marked difference again occurred in the 12-24 hour period. At this time, the CI in patients treated with the crystalloid solution alone was one-half that of the colloid-crystalloid group ( $2.75 \pm 0.25$  versus  $4.67 \pm 0.27$  L/min/m<sup>2</sup>,  $p < 0.0001$ ).

Table 10. Echocardiographic Cardiac Index during Postburn Volume Resuscitation

Group	Time Period (Hr)		
	0-12	12-24	24-48
I	$3.05 \pm 0.43$	$4.67 \pm 0.27^*$	$4.42 \pm 0.13$
II	$3.11 \pm 0.21$	$2.75 \pm 0.25^\dagger$	$4.03 \pm 0.40^\S$

Values = mean  $\pm$  1 SEM; \*  $p < 0.005$ , 0-12 hr vs 12-24 hr;  $^\dagger$   $p < 0.0001$ , Group II vs Group I;  $^\S$   $p < 0.05$ , 0-12 hr vs 24-48 hr; normal ECHO CI =  $3.4 \pm 0.04$  L/min/m<sup>2</sup>

Group II patients had a significantly decreased left ventricular (LV) end diastolic volume index (EDVI) and stroke index (SI) in the 12-24 hour period when compared to Group I (EDVI: Group I,  $56 \pm 3$  cc/m<sup>2</sup> versus Group II,  $36 \pm 4$  cc/m<sup>2</sup>,  $p < 0.01$ ; SI: Group I,  $40 \pm 2$  cc/bt/m<sup>2</sup> versus Group II,  $27 \pm 2$  cc/bt/m<sup>2</sup>,  $p < 0.01$ ). These were obtained simultaneously with CI measurements and indicate a decreased intravascular volume. Again, these volume measurements were not different after the addition of colloid to the therapy of Group II (Table 11).

The LV ejection indices corresponding to the above time periods are listed in Tables 12 and 13. Ejection fractions were normal throughout the entire study, while the mean rate of internal fiber shortening ( $V_{cf}$ ) was hypercontractile (normal =  $1.22 \pm 0.06$  circ/sec,  $p < 0.01$ ). Even when the CI was inadequate in Group II, the ejection indices were excellent. No evidence of abnormal intrinsic myocardial function could be recognized by this method.



Table 11. Left Ventricular Volume Data during Postburn Fluid Resuscitation

Time Period (Hr)	Group	EDVI	SI
0-12	I	42 ± 6	32 ± 5
	II	43 ± 3	34 ± 2
12-24	I	56 ± 3	40 ± 2
	II	36 ± 4*	27 ± 2*
24-48	I	52 ± 3	39 ± 2
	II	51 ± 4	37 ± 3

Values = mean ± 1 SEM; \* p < 0.001, Group I vs Group II; EDVI = end diastolic volume index, cc/m<sup>2</sup>; SI = stroke index, cc/bt/m<sup>2</sup>; normal ECHO EDVI = 60 ± 15, SI = 44 ± 10

Table 12. Left Ventricular Ejection Fraction during Postburn Fluid Resuscitation

Group	Time Period (Hr)		
	0-12	12-24	24-48
I	0.78 ± 0.02	0.74 ± 0.01	0.75 ± 0.02
II	0.79 ± 0.02	0.75 ± 0.02	0.75 ± 0.02

Values = mean ± 1 SEM; normal ECHO ejection fraction = 0.74 ± 0.02

Table 13. Left Ventricular Mean Rate of Internal Fiber Shortening during Postburn Fluid Resuscitation

Group	Time Period (Hr)		
	0-12	12-24	24-48
I	1.59 ± 0.16	1.86 ± 0.11*	1.64 ± 0.14
II	1.72 ± 0.08*	1.68 ± 0.10	1.70 ± 0.09

Values = mean ± 1 SEM; normal ECHO  $V_{cf}$  (circ/sec) = 1.22 ± 0.06; \* p < 0.01 when compared to normal

## DISCUSSION

Essential to the initial therapy of severe thermal injury is the early restoration of effective cardiovascular dynamics. In this study, postburn change in cardiac output (CO) and its relationship to LV volume was directly dependent upon the type of fluid composition utilized for resuscitation. Cardiovascular performance profiles revealed low CO, mildly decreased LV volume, and hypercontractile LV ejection dynamics in the early postburn period (0-12 hours). This occurred whether crystalloid alone or crystalloid combined with colloid was used for rehydration. The profiles in the middle postburn time period (12-24 hours) revealed normal CO, LV ejection dynamics, and LV volume in the colloid-treated patients, while crystalloid therapy alone resulted in low CO and LV volume. In the latter, LV ejection dynamics revealed no evidence of myocardial depression. In the late postburn time period (24-48 hours), the profiles showed a normal to high CO without any evidence of myocardial depression in both groups. In this time frame, all patients received colloid.

The majority of patients rehydrated with crystalloid solution failed to achieve a normal CO within the first 24 hours even though given an equivalent amount of replacement fluid (compared to the colloid group). Furthermore, they exhibited hypercontractile LV performance (high  $V_{cf}$ ) and normal ejection fractions. Therefore, myocardial depression could not be implicated as an etiology of their low CO. Their LV volume was decreased coincidentally with their decreased CO and indicated an inability to maintain intravascular volume.

Patients given colloid re-established a normal CO within 12-16 hours postburn. They maintained this level throughout the study period (48 hours). Their LV volume and ejection dynamics were never abnormal. The addition of colloid to Group II patients at the end of 24 hours postburn initiated a prompt cardiovascular recovery of CO and LV volume. Therefore, in this study the ability to re-establish a normal hemodynamic pattern after severe thermal injury was enhanced by the early infusion of colloid. This appears to be directly related to adequate volume repletion and intravascular retention.

The hemodynamic recovery profiles in the colloid-treated group are similar to those reported by Shoemaker et al (7). They also noted a return of normal to high CO in the "middle postburn period." They speculated, on the basis of LV function curves, that this represented enhanced myocardial performance. However, our study shows that LV ejection indices were high in the early postburn period and remained unchanged for the duration of the study.

In their patients, they distinguished two groups on the basis of hemodynamic response, one being designated as a "rapidly fatal burn injury." The present patient population does not confirm this classification in the colloid group. All patients treated in this group, including 9 with greater than 80% TBSB, remained hemodynamically stable for 48 hours postburn. However, four patients in the crystalloid group died within this period, and none attained an adequate CO. Their LV ejection dynamics were supracontractile, while their LV volumes were consistent with a decreased intravascular volume. These patients sustained impressive inhalation injuries and required massive crystalloid resuscitation. It is speculated that this was actually detrimental to their early clinical course. This was most likely secondary to a marked decrease in colloid oncotic pressure and further loss of intravascular volume (22).

The crystalloid-treated patients in the present study had comparable temporal restoration of their CO to those reported by Baxter. However, the clinical characteristics, percent in each study group, time from burn to study and death, autopsy results, and measurement intervals are not reported for his population. No matched group of patients was treated with colloid. However, when viewed as a group, his patients with greater than 40% TBSB failed to achieve a normal CO in 24 hours. Therefore, the conclusion that crystalloid therapy alone is the most advantageous resuscitative regimen seems unwarranted.

The finding that no patient exhibited abnormal LV ejection fraction or  $V_{cf}$  is convincing evidence against the presence of a clinical myocardial depressant factor. Even those patients with markedly inadequate CO failed to show myocardial depression. The volume-CO response tended to parallel changes in  $V_{cf}$ , but on the whole the ventricles remained maximally stimulated. Even in those patients with greater than 80% TBSB, LV performance was excellent. The recommendation that an inotropic agent would be beneficial in early postburn therapy (23) is disputed by these findings.

The clinical implication of the present study is that post-burn resuscitation therapy with a continuous infusion of a colloid component more rapidly and efficiently restores CO and LV intravascular volume. This occurred without a detrimental effect on LV

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intrinsic myocardial performance. Furthermore, inotropic agents have no scientific place in early postburn therapy if preburn cardiovascular function is normal. Although some patients can be effectively resuscitated with crystalloid therapy alone, they cannot be predicted on an individual basis. Either therapeutic approach is effective in TBSB of less than 30% burn if uncomplicated by inhalation injury.

#### PRESENTATIONS

Dorethy JF: Burn resuscitation monitoring by echocardiography. Thirtieth Anniversary Symposium, US Army Inst of Surgical Research, San Antonio, TX, 24 June 1977.

Dorethy JF: Evaluation of left ventricular function during early postburn resuscitation: Lack of evidence for a clinical myocardial depressant factor. Accepted for presentation, 1978 Annual Meeting, American Burn Association, Birmingham, Alabama, 1 April 1978.

#### PUBLICATIONS

None.



PROGRESS REPORT

PROJECT NO: 3S1611102BS05-00, MILITARY BURN RESEARCH

REPORT TITLE: THE HEMODYNAMIC RESPONSE TO THERMAL INJURY IN BURNED  
SOLDIERS -- II. LEFT VENTRICULAR PERFORMANCE IN ACUTE  
RESPIRATORY FAILURE TREATED WITH CONTINUOUS POSITIVE  
PRESSURE VENTILATION

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1 October 1976 - 30 September 1977

Investigators:

James F. Dorethy, M.D., Major, MC  
Victor Lam, M.D., Major, MC

Reports Control Symbol MEDDH-288(R1)

UNCLASSIFIED

# ABSTRACT

PROJECT NO: 3S1611102BS05-00, MILITARY BURN RESEARCH

REPORT TITLE: THE HEMODYNAMIC RESPONSE TO THERMAL INJURY IN BURNED SOLDIERS -- II. LEFT VENTRICULAR PERFORMANCE IN ACUTE RESPIRATORY FAILURE TREATED WITH CONTINUOUS POSITIVE PRESSURE VENTILATION

US Army Institute of Surgical Research, Brooke Army Medical Center, Fort Sam Houston, Texas 78234

Period covered in this report: 1 October 1976 - 30 September 1977

Investigators: James F. Dorethy, M.D., Major, MC  
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A decrease in cardiac output (CO) is often noted in patients treated with continuous positive pressure ventilation (CPPV). Controversy exists as to whether this is secondary to decreased left ventricular (LV) filling volume or myocardial depression. Fifteen echocardiographic (ECHO) studies were performed on 11 thermally injured patients requiring CPPV (20 cm H<sub>2</sub>O) for acute respiratory failure secondary to sepsis. Forty-five percent of the patients (5/11) exhibited an immediate reduction in ECHO end diastolic volume with the institution of 20 cm CPPV (20% decrease). Their ECHO-CO fell (22% decrease), and thermodilution (TD) CO also fell (27% decrease). These returned to control levels post-CPPV. The LV ECHO ejection indices remained unchanged. In the other six patients, no detectable changes occurred in their CO (ECHO and TD), ECHO end diastolic volume, ejection fraction, or mean rate of internal fiber shortening with 20 cm CPPV.

It is concluded that the fall in CO with CPPV is best explained by a decrease in LV end diastolic volume and not by an adverse effect on intrinsic myocardial contractility. This suggests that myocardial depression is not present and that the decreased CO is a manifestation of CPPV-induced volume change.

Burn injury  
Cardiac output  
Echocardiography  
Cardiovascular hemodynamics

THE HEMODYNAMIC RESPONSE TO THERMAL INJURY IN BURNED SOLDIERS --  
II. LEFT VENTRICULAR PERFORMANCE IN ACUTE RESPIRATORY FAILURE  
TREATED WITH CONTINUOUS POSITIVE PRESSURE VENTILATION

Inhalation injury sustained during thermal injury is associated with varying degrees of respiratory insufficiency. Continuous positive pressure ventilation (CPPV) is widely used in the treatment of this condition (1). The effects of such therapy on cardiopulmonary performance as well as the definition of "optimal CPPV" are controversial (2-6). The accurate assessment and manipulation of cardiopulmonary function during CPPV are difficult, because of the complex interaction of pleural, alveolar, and vascular pressures (7-9).

Some clinical studies have implied that left ventricular (LV) dysfunction is often a consequence of CPPV of greater than 15 cm

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H<sub>2</sub>O (8,10). However, experimental animal studies have noted no evidence of intrinsic LV dysfunction with CPPV (11-12). This study evaluated echocardiographic (ECHO) LV function during the utilization of CPPV for the treatment of acute respiratory failure as a complication of thermal injury.

#### METHODS

Eleven thermally injured patients with acute respiratory failure were studied on 15 separate occasions. All patients were on volume cycled ventilators. Serial ECHO studies were performed at 1 to 5 minute intervals in the following phases:

Pre-CPPV - 30 min  
10 cm CPPV - 20 min  
20 cm CPPV - 20 min  
Post-CPPV - 30 min

Simultaneous invasive monitoring was obtained in seven of 15 studies. No ECHO changes occurred at 10 cm of CPPV that were not also manifested or exaggerated at 20 cm CPPV. Therefore, data were analyzed in the pre-, 20 cm and post-CPPV phases. Left ventricular function was evaluated by ECHO end diastolic volume (EDV, cc), stroke volume (SV, cc/bt), cardiac output (CO, L/min), ejection fraction, and mean rate of internal fiber shortening ( $V_{cf}$ , circ/sec). Statistical analysis was performed using a Student t-test for unpaired data.

ECHO measurements were performed using an Echoline 20A ultrasound transducer interfaced with a 1858 Honeywell recorder. Variable transducer sizes were utilized when necessary for better ECHO definition. A standard M-mode ECHO scan was performed according to Popp et al (13). ECHO volumes and ejection indices were calculated by digitizing several beats during both inspiration and expiration. A Hewlett-Packard programmable 9830 desk computer was used for analysis.

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11. Qvist J, Pontoppidan H, Wilson RS, Lowenstein E, Laver MB: Hemodynamic responses to mechanical ventilation with PEEP: The effect of hypervolemia. *Anesthesiology* 42:45-55, 1975.

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A representative ECHO study is shown in Figure 1. Representative LV volume and diameter curves are shown in Figures 2 and 3.

Thermodilution CO was performed with a right-sided balloon guided catheter. These were obtained simultaneously with ECHO studies.

## RESULTS

### Patient Population

The patients were arbitrarily divided into two groups based on the response of their LV EDV to the use of 20 cm CPPV. Group I (n = 6 patients) had no statistical ( $p < 0.05$ ) decrease in LV EDV with 20 cm CPPV. Group II had an immediate and sustained decrease ( $p < 0.05$ ) in LV EDV with 20 cm CPPV. The characteristics of each group are listed in Table 1. The patients were young (mean age  $30 \pm 11$ ) with severe thermal injury ( $58 \pm 12$  percent total body surface burn). All of the patients subsequently died, and autopsy was obtained in 9/11. One patient in Group I had right sided staphylococcal endocarditis. One patient in Group II had myocardial abscesses and idiopathic fibrinous pericarditis. None of the patients had coronary artery disease. Thermodilution CO was obtained in seven of 15 studies.

Table 1. Patient Characteristics

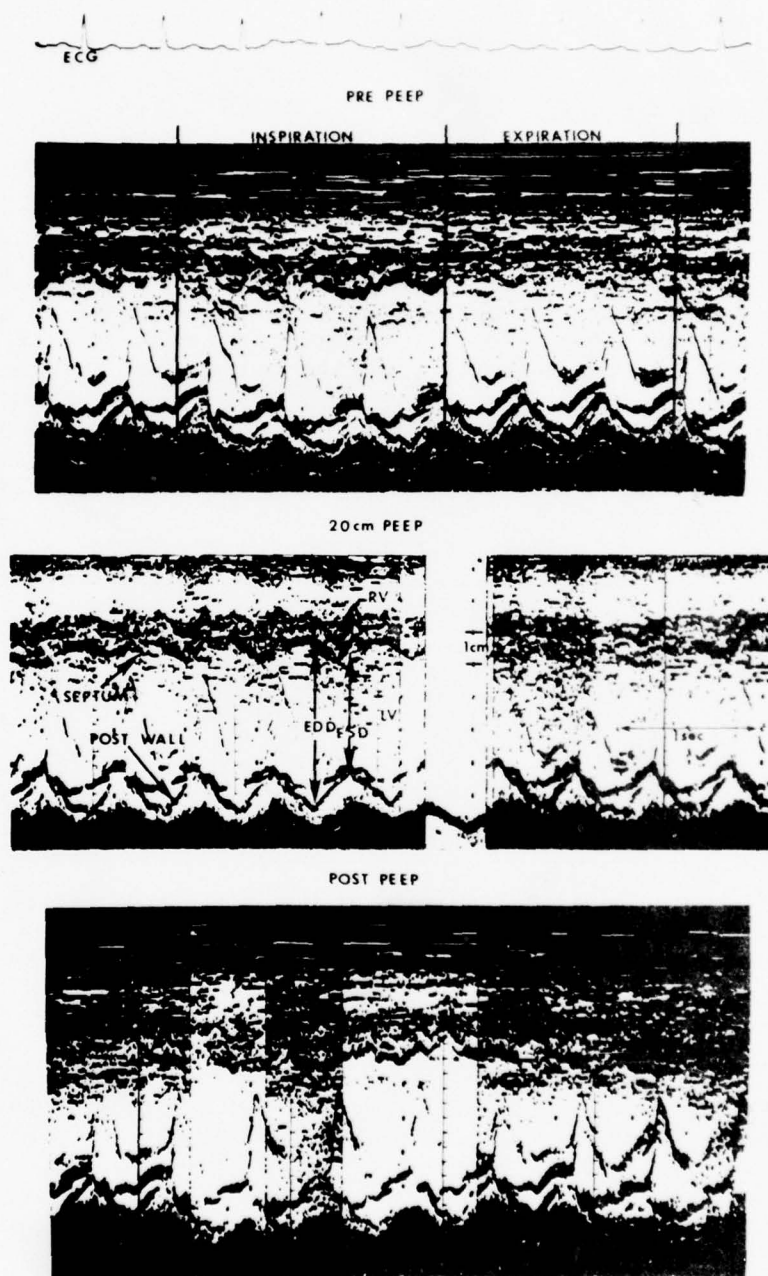
	Group I	Group II	Total
n	6	5	11
n Studies	9	6	15
Age (yr)	$27 \pm 7$	$35 \pm 13$	$30 \pm 11$
TBSB (%)	$60 \pm 13$	$54 \pm 12$	$58 \pm 12$
Autopsy	5/6	4/5	9/11
TD-CO	5/9	2/6	7/15

n = number of patients; n studies = number of studies; values = mean  $\pm$  1 SD; TBSB = total body surface burn; TD-CO = thermodilution cardiac output

### Etiology of Respiratory Failure

The complicating clinical factors and etiology of respiratory failure in these patients are listed in Table 2. Five of 11 (45%) patients had moderate to severe smoke inhalation injury. This is diagnosed in our unit by direct bronchoscopy, xenon scan, and arterial blood gases. In nine of 11 (82%), severe sepsis was present.

Figure 1  
ECHOCARDIOGRAPHY IN ACUTE RESPIRATORY  
FAILURE TREATED WITH PEEP



# ECHOCARDIOGRAPHIC LEFT VENTRICULAR VOLUME

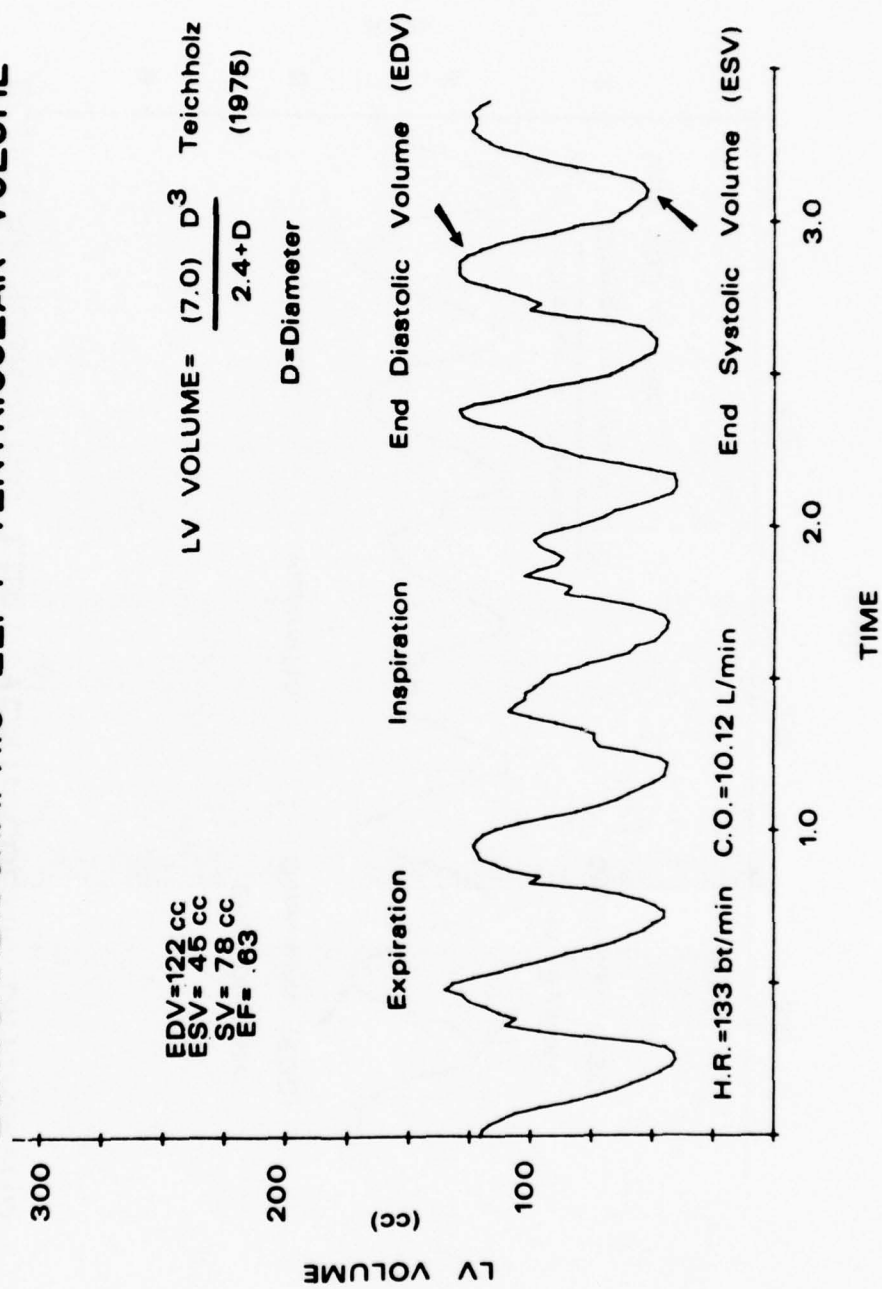


Figure 2

# ECHOCARDIOGRAPHIC LEFT VENTRICULAR DIMENSIONS

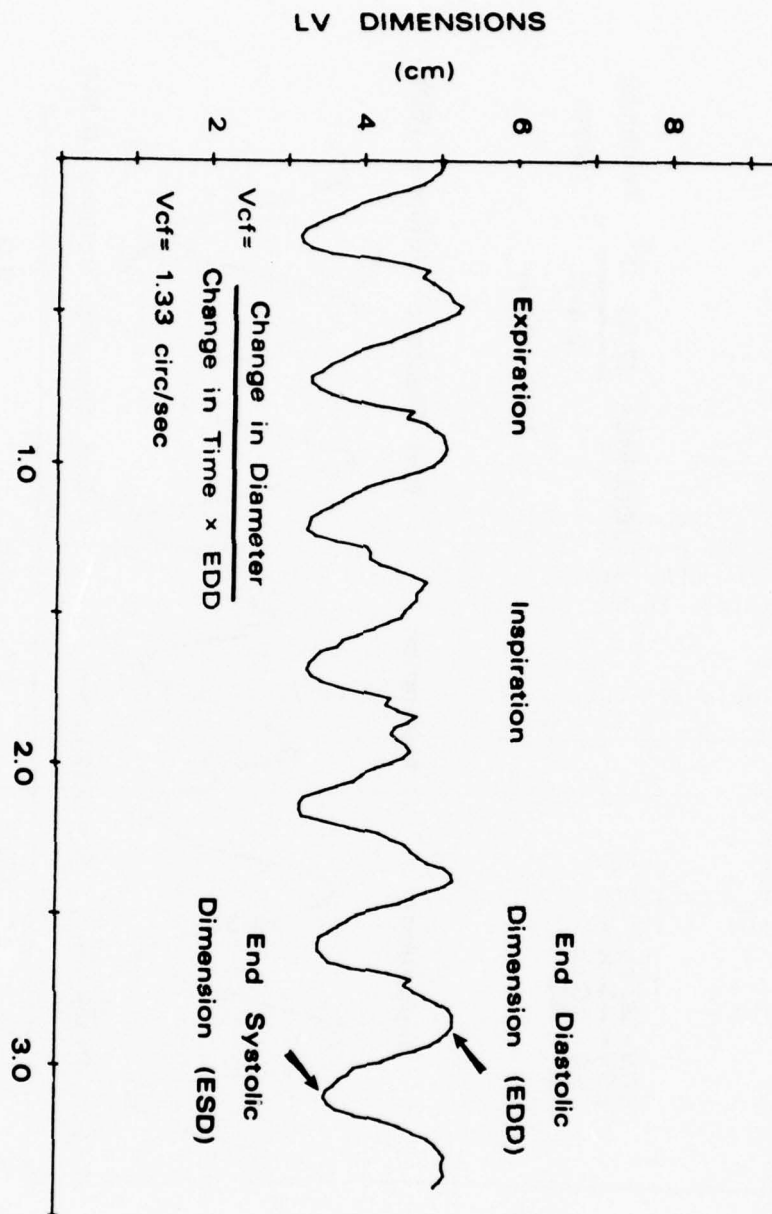


Figure 3



One patient in each group exhibited respiratory failure in response to volume overload.

Table 2. Etiology of Respiratory Failure

	Group I	Group II	Total (%)
n	6	5	11 (100)
Inhalation injury	3	2	5 (45)
Sepsis	5	4	9 (82)
Gram (-)	2	1	3 (27)
Mixed (-) & (+)	3	3	6 (55)
Volume overload	1	1	2 (18)

n = number of patients

#### Pre-CPPV Left Ventricular Function

Table 3 compares left ventricular function in the two groups in the pre-CPPV phase. In Group I, which by definition had no decrease in EDV with CPPV, three of six patients had abnormal ejection fractions of less than 59%. Only one patient had a markedly elevated EDV.

Table 3. Comparison of ECHO LV Function Prior to CPPV

	Group I	Group II	Total (%)
n	6	5	11 (100)
EF < 0.59	3/6	0/5	3/11 (27)
$V_{cf}$ < 1.00	0/6	0/5	0/11 (0)
EDV > 178 cc	0/6	1/5	1/11 (9)
SV < 36 cc/bt	1/6	0/5	1/11 (9)
E-CO < 3.8 L/min	0/6	0/5	0/11 (0)
E-CO > 9.8 L/min	3/6	3/5	6/11 (55)

n = number of subjects; EF = ejection fraction,  $V_{cf}$  = mean rate of internal fiber shortening (circ/sec); EDV = end diastolic volume; SV = stroke volume; E-CO = ECHO cardiac output

Six of 11 (55%) patients had cardiac outputs that were elevated. This is a consistent finding in our septic patients during the hyperdynamic or pyrogenic phase of persistent bacteremia. None of the patients had abnormally low CO.

Table 4 summarizes the ECHO findings in these two groups prior to CPPV, at 20 cm CPPV, and after its discontinuance. Heart rates did not change significantly in either group during the addition of CPPV.

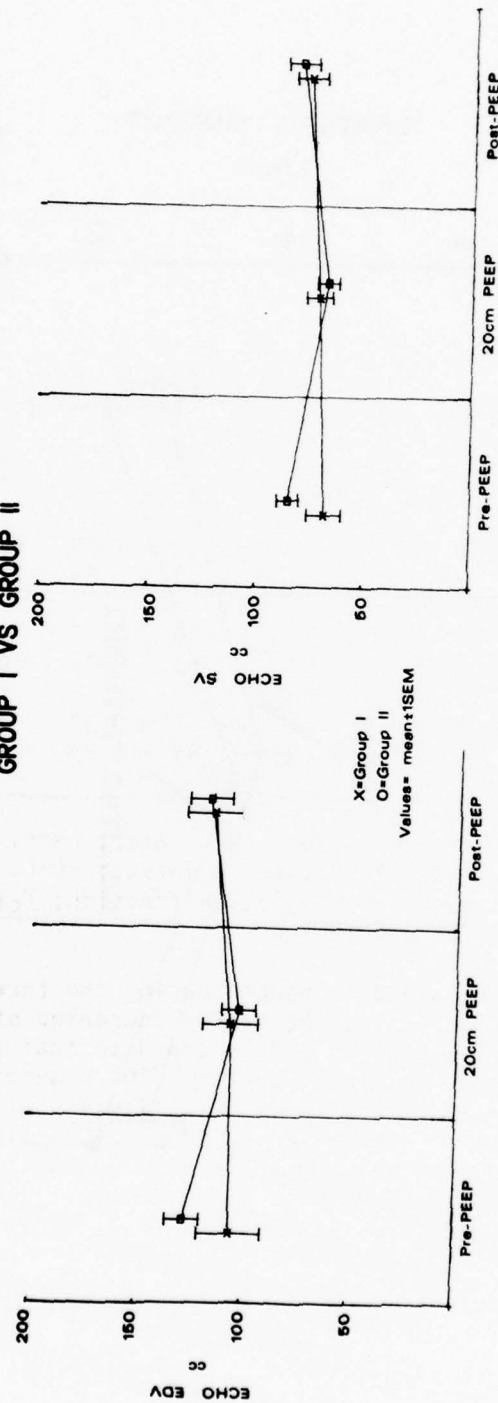
Table 4. ECHO End Diastolic Volume and Ejection Indices during Continuous Positive Pressure Ventilation

	Group	Pre-CPPV	20 cm CPPV	Post-CPPV
HR (bt/min)	I	125 ± 16	122 ± 16	124 ± 13
	II	124 ± 14	126 ± 15	129 ± 18
EDV (cc)	I	106 ± 44	107 ± 40	116 ± 40
	II	128 ± 32	103 ± 36*	118 ± 41
E-CO (L/min)	I	8.87 ± 3.32	8.79 ± 3.09	9.49 ± 3.29
	II	10.63 ± 3.24	8.27 ± 2.84*	10.58 ± 3.24
TD-CO (L/min)	I	9.81 ± 3.25	10.31 ± 4.05	10.48 ± 3.74
	II	11.80 ± 2.26	8.85 ± 0.64*	11.75 ± 1.63
EF	I	0.67 ± 0.14	0.70 ± 0.12	0.67 ± 0.13
	II	0.67 ± 0.04	0.65 ± 0.05	0.68 ± 0.03
$V_{cf}$ (circ/sec)	I	1.44 ± 0.36	1.55 ± 0.33	1.50 ± 0.33
	II	1.47 ± 0.36	1.47 ± 0.29	1.56 ± 0.25

Values = mean ± 1 SD; \*  $p < 0.025$ ; HR = heart rate; EDV = end diastolic volume; E-CO = ECHO cardiac output; TD-CO = thermodilution cardiac output; EF = ejection fraction;  $V_{cf}$  = mean rate of internal fiber shortening

EDV in Group I remained unchanged during the three study phases. However, in Group II patients, the LV EDV decreased statistically from  $128 \pm 32$  cc to  $103 \pm 36$  cc and returned to near control levels post-CPPV (Figure 4A). This represented a 20% change and occurred within the first few minutes after the institution of CPPV. Stroke volume changed in a similar direction (Figure 4B). This paralleled the decrease in ECHO CO (22%) and was consistent with that noted by thermodilution CO. The decrease in CO (Group II) was similar when measured with thermodilution or ECHO (Figure 5). None of the patients in either group exhibited an increased LV EDV. The LV ejection dynamics as measured by ECHO ejection fraction and  $V_{cf}$  showed no deterioration in either group during CPPV therapy (Figures 6A and 6B).

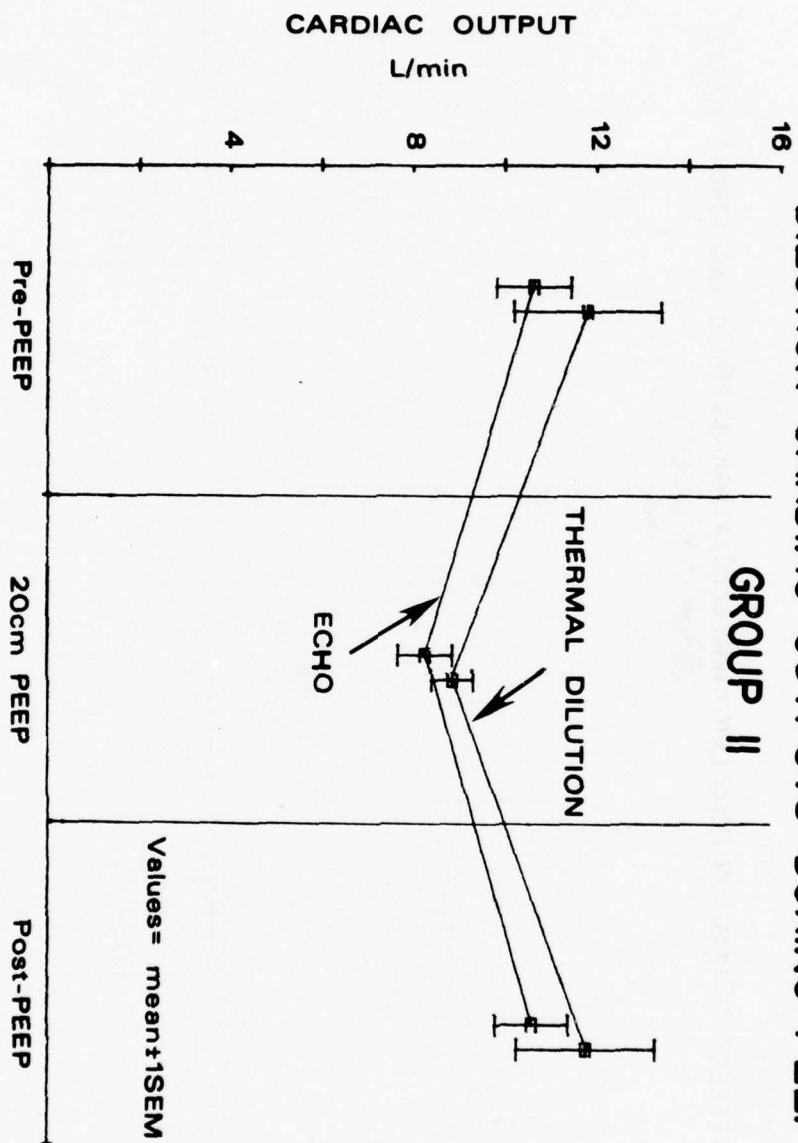
# EFFECT OF PEEP ON ECHO LEFT VENTRICULAR END DIASTOLIC AND STROKE VOLUME GROUP I VS GROUP II



STUDY PHASE  
Figure 4A

STUDY PHASE  
Figure 4B

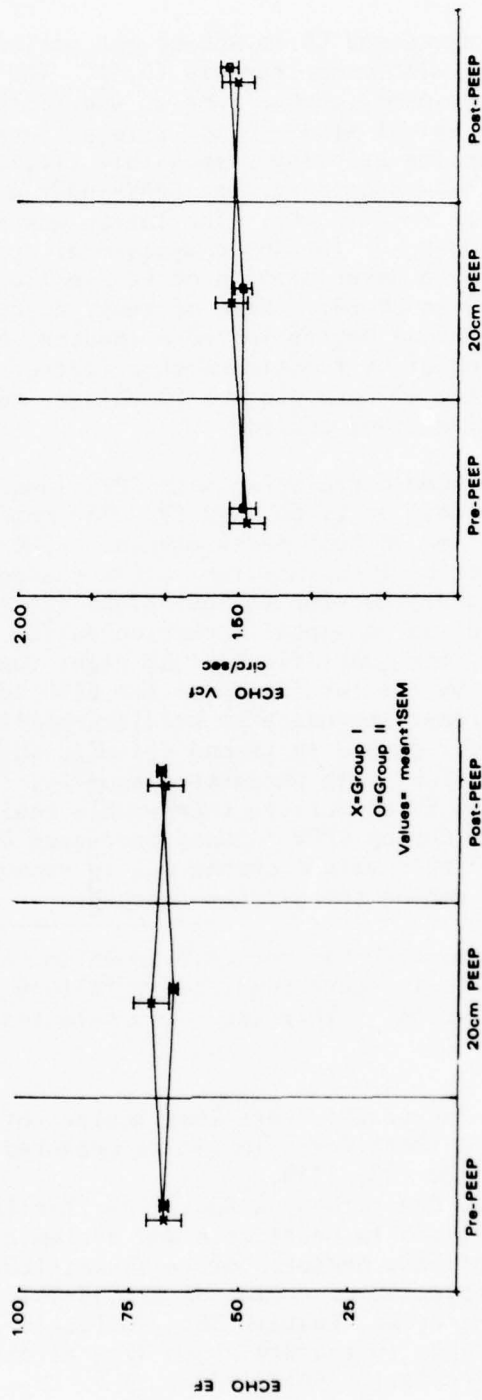
# CORRELATION BETWEEN ECHO AND THERMAL DILUTION CARDIAC OUTPUTS DURING PEEP



STUDY PHASE  
Figure 5



# EFFECT OF PEEP ON ECHO LEFT VENTRICULAR EJECTION INDICIES GROUP I VS GROUP II



STUDY PHASE  
Figure 6B

STUDY PHASE  
Figure 6A

## DISCUSSION

The finding of a decreased CO in 45% of the patients treated with CPPV is consistent with other reports (2,5). The exact pathophysiology of this hemodynamic change remains undefined but clinically important. Most animal studies implicate an intrathoracic pressure-volume interaction as being responsible (11,12). However, several human studies have suggested that CPPV-induced myocardial depression plays a major role (8,10). The latter was not substantiated by the present findings. Intrinsic myocardial dysfunction would be readily identified by a deterioration of LV ejection fraction and  $V_{cf}$ , and/or an increase in LV EDV. None of these occurred during CPPV therapy. If myocardial depression were induced, one would expect a gradual worsening of LV function with a further decrease in CO. In our patients, the CO response was immediate, remaining at the same level for the entire study period.

The only positive ECHO correlation with CPPV-induced CO decrease was a simultaneous decrease in LV EDV and SV. The magnitude as a percent change was similar in both measurements. ECHO EDV has been shown to be an indicator of intravascular volume change in physiologic and pharmacologic cardiovascular manipulations (14-16). The only qualitative ECHO change was in septal excursion during phasic respiration. Unfortunately, the quantification of right ventricular dimensions was limited by the resolution of the ECHO technique. An artifactual volume decrease secondary to cardiac rotation is ruled out by the nonstatistical change in LV end systolic volume. A rotational artifact would affect both parameters equally. Therefore, the change in LV EDV and SV appears to represent a real phenomenon and was only recognized during CPPV-induced decreased CO. This study did not discern whether this volume change was in venous return or secondary to pulmonary venous capacitance changes.

Prior to this study, ECHO has not been shown to be useful in evaluating LV performance in acute respiratory failure or its therapy. The patient population in this study was selected on the basis

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of adequate pre-respiratory failure echograms, and technically good serial studies were easily obtained during the CPPV protocol. The adequacy of this technique in all patients with respiratory failure remains unknown.

The only technical problem encountered was the continuous recording during phasic respiration. The appearance of dense anterior echoes during inspiration was a common problem. These are similar to changes in noncritically ill patients (17). The problem could usually be resolved by changing transducer angulation or interspace. The serial studies in each individual were performed at their established ECHO "window." The magnitude of pre-CPPV LV dimension changes varied in individual patients, but none was as marked as noted by Fenichel et al (17). A recent description of phasic respiratory changes in a normal ECHO population suggests that the inspiratory LV EDV decrease is secondary to posterior displacement of the septum (18). This qualitative change was markedly exaggerated in these patients with acute respiratory failure and was usually associated with a marked pulsus paradoxus. Beat-by-beat analysis of ECHO SV revealed a significant increase in expiratory ejection volume. Continuous PPV tended to eliminate or blunt these phasic changes. This suggests that an inspiratory increase in right ventricular volume encroaches on the LV cavity. The significance of the elimination of this phenomenon by CPPV and its relation to the decreased CO is unknown.

This study did not evaluate net intravascular pressure changes. Therefore, no pressure-volume profiles during CPPV were attempted. Right-sided pressures were variable pre-CPPV and showed no consistent or predictable change with 20 cm CPPV. This is a meaningless measurement without an estimate of intrathoracic and airway pressures. Additionally, no pulmonary compliance measurements were performed. This variable needs to be considered in future protocol designs.

This study shows that echocardiography is feasible for the evaluation of LV performance during the treatment of acute respiratory failure with CPPV. It adds a new dimension to the study of complex intrathoracic pressure-volume relationship during such therapy. The finding that intravascular volume changes in the thorax corresponded to CO measurements is helpful in understanding this basic clinical therapy and its complications. The future clinical applicability of

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this method requires correlation of ECHO indices to net intravascular pressure changes and direct measurements of LV filling pressure.

#### PUBLICATIONS

Dorethy JF, Lam V: The effect of positive end expiratory pressure (PEEP) on left ventricular (LV) function in patients with respiratory failure (Abstract). Chest 72:398, 1977.

Dorethy JF, Lam V: Left ventricular performance determined by echocardiography during continuous positive pressure ventilation for adult respiratory distress syndrome (Abstract). Am Rev Resp Dis 115: 101, 1977.

Dorethy JF, Lam V: Left ventricular volume and ejection indices during positive end expiratory pressure (Abstract). Accepted for publication, Circulation Supplement, October 1977.

#### PRESENTATIONS

Dorethy JF: The effect of positive end expiratory pressure (PEEP) on left ventricular (LV) function in patients with respiratory failure. Accepted for presentation, American College of Chest Physicians 43rd Annual Scientific Assembly, Las Vegas, Nevada, November 1977.

Dorethy JF: Left ventricular volume and ejection indices during positive end expiratory pressure. Accepted for presentation, American Heart Association 50th Annual Scientific Sessions, Miami Beach, Florida, November 1977.



RESEARCH AND TECHNOLOGY WORK UNIT SUMMARY				1. AGENCY ACCESSION <sup>a</sup>	2. DATE OF SUMMARY <sup>a</sup>	REPORT CONTROL SYMBOL DD-DR&E(AR)536	
3. DATE PREV. SUMM <sup>a</sup>	4. KIND OF SUMMARY	5. SUMMARY SCTY <sup>a</sup>	6. WORK SECURITY <sup>a</sup>	7. REGRADING <sup>a</sup>	8A. DISSEM INSTN <sup>a</sup>	8B. SPECIFIC DATA- CONTRACTOR ACCESS	9. LEVEL OF SUM <sup>a</sup>
76 10 01	D. CHANGE	U	U	NA	NL	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	A. WORK UNIT
10. NO./CODES <sup>a</sup>	PROGRAM ELEMENT	PROJECT NUMBER	TASK AREA NUMBER	WORK UNIT NUMBER			
A. PRIMARY	61102A	3S1611102BS05	00	083			
B. CONTRIBUTING							
C. CONTRIBUTING							
11. TITLE (Precede with Security Classification Code) <sup>a</sup>							
(U) Gastrointestinal Alterations and Complications in Burned Troops (44)							
12. SCIENTIFIC AND TECHNOLOGICAL AREAS <sup>a</sup>							
003500 Clinical Medicine							
13. START DATE		14. ESTIMATED COMPLETION DATE		15. FUNDING AGENCY		16. PERFORMANCE METHOD	
76 10		Cont		DA		C. In-House	
17. CONTRACT/GRANT Not Applicable				18. RESOURCES ESTIMATE			
A. DATES/EFFECTIVE:				PRECEDING			
B. NUMBER:				FISCAL YEAR			
C. TYPE:				CURRENT			
D. KIND OF AWARD:				E. CUM. AMT.			
19. RESPONSIBLE DOD ORGANIZATION				20. PERFORMING ORGANIZATION			
NAME: US Army Institute of Surgical Research				NAME: US Army Institute of Surgical Research			
ADDRESS: Ft Sam Houston, Tx 78234				Surgical Study Branch			
RESPONSIBLE INDIVIDUAL				PRINCIPAL INVESTIGATOR (Furnish SSAN if U.S. Academic Institution)			
NAME: Basil A Pruitt, Jr, COL, MC				NAME: Hugh P McElwee, MAJ, MC			
TELEPHONE: 512-221-2720				TELEPHONE: 512-221-6532			
31. GENERAL USE				SOCIAL SECURITY ACCOUNT NUMBER:			
FOREIGN INTELLIGENCE NOT CONSIDERED				ASSOCIATE INVESTIGATORS			
				NAME: Barry A Levine, MAJ, MC			
				NAME: Kenneth R Sirinek, MAJ, MC			
				DA			
22. KEY WORDS (Precede EACH with Security Classification Code)							
(U) Burn injury; (U) Infection; (U) Curling's ulcer; (U) Gastritis; (U) Pepsinogen;							
(U) Small bowel; (U) Intestinal flora; (U) Intestinal absorption							
23. TECHNICAL OBJECTIVE, 24. APPROACH, 25. PROGRESS (Furnish individual paragraphs identified by number. Precede text of each with Security Classification Code)							
23. (U) To document and evaluate the gastrointestinal changes in burned soldiers. To study the role of pepsinogen in the etiology of Curling's ulcer and the effectiveness of cimetidine in ulcer prophylaxis. To assess the role of infection on stress ulcers and changes in small bowel morphology and function. To evaluate etiologies of stress ulcers.							
24. (U) Esophageal, gastric and duodenal mucosal lesions will be verified endoscopically and with biopsies in burn patients. Mucosal lesions will be related to serum pepsinogen levels and the effect of cimetidine determined. Small bowel structure and function will be evaluated and the effect of bacterial flora assessed. A laboratory animal model of stress ulcer will be developed.							
25. (U) 76 10 - 77 09 Serial endoscopic evaluations have been completed on 22 patients. Serum pepsinogen levels increased markedly in two patients with subsequent hemorrhage. Cimetidine is being evaluated in a double-blind fashion. Animal models have been developed and are being utilized to evaluate further the pathogenesis and treatment of stress ulcers. Animal models are being developed to assess small bowel structure, function and associated change in bacterial flora.							

<sup>a</sup>Available to contractors upon estimator's approval.

DD FORM 1498  
1 MAR 68

PREVIOUS EDITIONS OF THIS FORM ARE OBSOLETE. DD FORMS 1498A, 1 NOV 66 AND 1498-1, 1 MAR 68 (FOR ARMY USE) ARE OBSOLETE.

PROGRESS REPORT

PROJECT NO. 3S1611102BS05-00, MILITARY BURN RESEARCH

PROJECT TITLE: GASTROINTESTINAL ALTERATIONS AND COMPLICATIONS IN  
BURNED TROOPS

US ARMY INSTITUTE OF SURGICAL RESEARCH  
BROOKE ARMY MEDICAL CENTER  
FORT SAM HOUSTON, TEXAS 78234

1 October 1976 - 30 September 1977

Investigators:

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Reports Control Symbol MEDDH-288(R1)

UNCLASSIFIED

ABSTRACT

PROJECT NO. 3S1611102BS05-00, MILITARY BURN RESEARCH

PROJECT TITLE: GASTROINTESTINAL ALTERATIONS AND COMPLICATIONS IN  
BURNED TROOPS

US Army Institute of Surgical Research, Brooke Army Medical Center,  
Fort Sam Houston, Texas 78234

Period covered in this report: 1 October 1976 - 30 September 1977

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This section of the Internal Medicine Branch performs clinical and laboratory research and provides consultative support in the area of gastroenterology.

Our current clinical research involves regular endoscopic evaluation of thermally injured patients with burns involving 30% or greater of the total body surface.

Laboratory research is directed at determining the etiologies of Curling's ulcers, and evaluating the physiology of  $H_2$ -receptor antagonists. We are also assessing the role of infection in stress ulceration and evaluating its effect on small bowel morphology and function.

Burn injury  
Curling's ulcer  
Small bowel  
Infection

## GASTROINTESTINAL ALTERATIONS AND COMPLICATIONS IN BURNED TROOPS

This report provides an overview of our current studies of gastrointestinal alterations and complications in burned troops.

We are performing serial endoscopic evaluation of thermally injured patients with burns involving 30% or greater of the total body surface. These findings are being tabulated for further definition of the natural history of stress lesions.

Little attention has previously been given to the role of pepsin digestion of the gastric mucosa following thermal injury. Currently, we are utilizing a radioimmunoassay of serum pepsinogen as a reflector of gastroduodenal morphology. A pilot study has been performed and indicated that serum pepsinogen levels rose markedly prior to gastrointestinal bleeding in two of 11 patients studied. We are currently evaluating the endoscopic appearance of the gastroduodenal mucosa and determining if correlation exists between the serum pepsinogen and the endoscopic appearance of the stomach. To date, we have evaluated 33 patients and performed 75 upper gastrointestinal endoscopies.

Since the presence of hydrochloric acid is essential in the experimental production of stress ulceration, control of hydrogen ion secretion by the gastric mucosa would seem a logical method of treatment. Histamine is felt to be the final common pathway in gastric acid secretion regardless of the stimulus employed. A new group of drugs has been developed which antagonizes the action of histamine on the parietal cells of the gastric mucosa. Cimetidine is a third generation histamine antagonist and is being given in a double-blind fashion to determine its effectiveness in prevention of gastroduodenal disease. We have studied 33 patients to date.

We continue to search for etiologic factors responsible for Curling's ulcer and investigate the physiology of  $H_2$ -receptor antagonists. To date, we have shown the effectiveness of cimetidine in the prevention of stress-induced gastric erosions in animals. We have also shown that pre-shock cimetidine protects against reductions in gastric mucosal blood flow in piglets. We are now embarking on studies designed to evaluate the role of the gastrointestinal system in host response to thermal injury and associated infections.

Erosive gastritis and stress ulceration of the gastroduodenal mucosa have significantly decreased in our patient population due to the use of an intensive antacid regimen. In a review of the gastrointestinal complications over the last two years, the incidence of complications of the small and large bowel has almost doubled from 2.6% during the 1960's to 4.9% from 1975 to 1977.



Four patients developed superior mesenteric artery (SMA) syndrome. Nasogastric suction, intravenous hyperalimentation, and positional feeding were used in all four cases. Resolution of the obstruction was accomplished in three cases, while the remaining patient succumbed to intervening burn wound sepsis.

Three patients developed pseudo-obstruction of the colon; all were initially managed nonoperatively. One eventually required celiotomy with cecostomy because of failure of medical management. There were nine cases of ischemic enterocolitis and one case of sigmoid volvulus.

These complications present an extremely complex differential diagnosis in the thermally injured patient and frequently are not established until abdominal exploration. Abdominal distension, altered bowel habits, and brisk rectal bleeding are early clinical signs of these disorders, yet are not diagnostic. Sepsis, renal insufficiency, respiratory problems, and mental confusion which frequently occur in patients with large burns further complicate this diagnostic dilemma.

The etiology of these complications is unknown and very difficult to define. Hypotension and hypoxemia were common in these patients. Bacterial overgrowth and microvascular thrombi were present in approximately one-half of the specimens examined. This is probably compounded by the necessary, frequent use of antibiotics and narcotics in this group of critically ill patients. Sepsis and splanchnic hypoperfusion have been postulated as pivotal pathophysiologic mechanisms in the development of these intestinal problems.

Because of the insidious onset of these complications and the precarious health of these patients, diagnosis is difficult and the margin of error is nil. Routine stool guaiac tests and stool cultures are performed. Conventional diagnostic modalities including proctosigmoidoscopy and conventional roentgenograms of the abdomen often fail to pinpoint the disease process. Contrast radiography and endoscopy must be utilized early and have been helpful in determining the site of bleeding in some of these patients.

#### PRESENTATIONS

Teegarden DK: Current gastrointestinal studies in burn patients. Thirtieth Anniversary Symposium, US Army Institute of Surgical Research, San Antonio, TX, 24 June 1977.

#### PUBLICATIONS

None.

PROGRESS REPORT

PROJECT NO. 3S1611102BS05-00, MILITARY BURN RESEARCH

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TROOPS -- SERUM PEPSINOGEN LEVELS IN THE THERMALLY INJURED  
SOLDIER: A POSSIBLE PREDICTOR OF GASTRODUODENAL DISEASE

US ARMY INSTITUTE OF SURGICAL RESEARCH  
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1 October 1976 - 30 September 1977

Investigators:

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Little attention has been directed to pepsin as an etiologic factor in ulcerative disease of the stomach and duodenum following thermal injury. Pepsin is a proteolytic enzyme that is formed from the cleavage of its precursor, pepsinogen. Its cells of origin are the chief cell and mucous neck cell in the stomach. Pepsinogen is a proteolytic enzyme which attacks soluble native proteins and is therefore an endopeptidase. Previous studies in duodenal ulcer disease and other diseases of the intestine have shown pepsinogen to increase prior to a gastrointestinal hemorrhage.

This study proposes to analyze serum pepsinogen levels and correlate these with serial endoscopic findings.

Burn injury  
Curling's ulcer  
Gastritis  
Pepsinogen

GASTROINTESTINAL ALTERATIONS AND COMPLICATIONS IN BURNED TROOPS --  
SERUM PEPSINOGEN LEVELS IN THE THERMALLY INJURED SOLDIER:  
A POSSIBLE PREDICTOR OF GASTRODUODENAL DISEASE

Little attention has been given pepsin as an etiologic factor in ulcerative disease of the stomach and duodenum. Pepsin, a proteolytic enzyme, attacks soluble native proteins within the molecule and is therefore an endopeptidase. It is present in its cells of origin, the chief cell and mucous neck cells, as a zymogen precursor called pepsinogen. Other unidentified cells also contain pepsinogens. A leakage of digestive enzymes into the blood stream is a common occurrence and can be used, for instance, in detecting diseases of the pancreas, utilizing the serum lipase and amylase. How pepsinogens gain access to the circulation is unknown; serum levels have been shown to reflect the secretory activity and morphologic status of mucosa and have been helpful in the diagnosis of pernicious anemia, duodenal ulcer, and gastric cancer.

Pepsinogens are separated by immunochemical methods into two groups: PGI and PGII. The two groups differ in mucosal distribution and cellular origins. Both groups are found in the fundic mucosa.

The purpose of this study is to analyze the predictive value of the stomach enzyme precursor, pepsinogen, as an indicator of gastroduodenal mucosal change following thermal injury.

Progress

Serial serum samples are submitted to Dr. Samloff's laboratory for analysis, utilizing a competitive binding double antibody radioimmunoassay.

In an 11-patient pilot study, two patients demonstrated elevated serum pepsinogen levels, one of which was associated with gastrointestinal hemorrhage.

We have completed 75 upper endoscopies on patients with a greater than 30% total body surface burn. The findings at these endoscopies have been number coded. We will compare our findings with the corresponding serum pepsinogen levels as determined by Dr. Samloff.

These correlations are in progress, but no specific conclusions can be drawn to date.

PUBLICATIONS AND/OR PRESENTATIONS

None.



PROGRESS REPORT

PROJECT NO: 3S1611102BS05-00, MILITARY BURN RESEARCH

REPORT TITLE: GASTROINTESTINAL ALTERATIONS AND COMPLICATIONS IN  
BURNED TROOPS -- THE EVALUATION OF CIMETIDINE, A  
NEW H<sub>2</sub>-RECEPTOR ANTAGONIST, IN THE PREVENTION OF  
STRESS ULCERATION FOLLOWING THERMAL INJURY

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Hemorrhage and perforation continue to be the most life-threatening gastrointestinal complications following thermal injury. Antacids are currently accepted as the prophylaxis of choice in the treatment of stress ulceration following a burn injury. Although effective, antacid therapy presents several therapeutic problems.

Cimetidine is an H<sub>2</sub>-receptor antagonist. It has been shown in several clinical trials to markedly inhibit gastric acid secretion in the stomach from multiple stimuli and is currently without known serious side effects. This protocol proposes to study the effectiveness of cimetidine in preventing and treating Curling's ulceration and compare its effectiveness to antacids.

Burn injury  
Curling's ulceration  
Cimetidine

## GASTROINTESTINAL ALTERATIONS AND COMPLICATIONS IN BURNED TROOPS -- THE EVALUATION OF CIMETIDINE, A NEW H<sub>2</sub>-RECEPTOR ANTAGONIST, IN THE PREVENTION OF STRESS ULCERATION FOLLOWING THERMAL INJURY

The exact pathophysiologic role of gastric acid in the production of Curling's ulceration has yet to be determined. However, stress ulceration fails to appear in the absence of gastric acid in the experimental animal.

Many investigators feel that histamine is the final common mediator of all modalities of gastric acid secretion regardless of the initial stimulus. Histamine stimulates contraction of smooth muscle of various organs such as the gut and bronchial tree, and these effects can be suppressed by low concentrations of standard antihistamines, such as mepyramine. The pharmacological receptors involved in the mepyramine-sensitive histamine responses have been defined as H<sub>1</sub>-receptors. Histamine also stimulates the secretion of gastric acid, increases the heart rate, and inhibits contraction of the uterine muscle. These actions cannot be antagonized by standard antihistamines and are considered to be due to stimulation of histamine receptors, defined as H<sub>2</sub>-receptors.

### METHODS

Fifty to 100 patients, age 16 or older, with greater than a 30% total body surface burn area, will be included in this study. All patients who provide informed consent will be followed with serial upper gastrointestinal endoscopies on or about postburn days 0, 3 and 10.

The patients will be randomly divided into two therapeutic groups. The study is double-blind. Each group will receive two forms of treatment. One group will receive cimetidine and a placebo simulating antacid in color and appearance but without meaningful buffering capacity. The other group will receive antacids (Mylanta II; buffering capacity is 4.1 mEq/cc) and a placebo simulating cimetidine but without properties affecting gastric acid secretion.

The purpose of this study is to compare the efficacy of cimetidine versus antacids in the prevention and treatment of Curling's ulceration.

### PROGRESS

To date, 33 patients have been entered into our study, and we have performed and coded over 75 upper endoscopies. We are also collecting serial data on acid secretion and clinical gastrointestinal bleeding. Since this is a double-blind random

study, we have not yet broken the code, and no data have been analyzed.

#### SUMMARY

We have made encouraging progress with this study and expect to complete our data collection within the next six months.

#### PUBLICATIONS AND/OR PRESENTATIONS

None.



FINAL REPORT

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BURNED TROOPS -- STUDIES ON THE ETIOLOGY AND THERAPY  
OF STRESS ULCERS IN AN ANIMAL MODEL SIMULATING THE  
BURNED SOLDIER: A. EVALUATION OF CIMETIDINE IN  
THE PREVENTION OF STRESS-INDUCED GASTRIC EROSIONS

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Acute gastric erosions following severe stress usually occur in the presence of gastric acid. Cimetidine (Smith Kline & French), an H<sub>2</sub>-receptor antagonist, inhibits both resting and stimulated acid production. This study investigated the effect of pre-treatment with cimetidine in preventing stress-induced erosions alone and those potentiated by gastric mucosal barrier breakers (GMBB).

Female C-D rats (Charles River Laboratories), weighing approximately 180 gm were stressed by a 72-hour fast, followed by 3 hours of restraint in a plastic cage (Fisher Scientific) in a cold room at 4° C. Thirty minutes prior to restraint, each rat received either cimetidine (Ci), 20 mg/kg, or normal saline (NS) intraperitoneally. Three trials were performed. The first (I) compared Ci to NS. The second (II) compared 15 mM taurocholate plus cimetidine (Tch + Ci) to both NS alone and to Tch + NS. The third (III) compared 20 mM aspirin + cimetidine (ASA + Ci) to NS and to ASA + NS. In trials II and III, a separate group of animals was fasted, given either Tch or ASA, but not restrained. Tch and ASA were given via an oro-gastric tube immediately prior to cold restraint.

Following the restraint period, each animal was sacrificed with pentobarbital. The stomach of the intact animal was injected with formalin and was then excised. Lesions of the glandular mucosa were counted under magnification (2.5X) and confirmed histologically with permanent sections.

In trial I, pre-treatment with cimetidine significantly reduced the incidence of gastric mucosal lesions (Table I). The

Scheffé modification of Analysis of Variance was used in making statistical comparisons between groups.

Table I

Trial	Treatment Group	Number	Lesions*	P
I	NS	22	8.4 ± 1.7	.001 <sup>a</sup>
	Ci	23	1.2 ± 0.5	
II	NS	10	5.5 ± 0.9	.05 <sup>a</sup> .01 <sup>a,b</sup> NS <sup>c</sup>
	Tch + NS	10	10.1 ± 1.1	
	Tch + Ci	11	0.5 ± 0.2	
	Tch, no restraint	6	0.2 ± 0.2	
III	NS	12	6.8 ± 1.6	.05 <sup>a</sup> .05 <sup>a</sup> , .01 <sup>b</sup> NS <sup>c</sup>
	ASA + NS	12	20.1 ± 2.7	
	ASA + Ci	14	2.2 ± 0.6	
	ASA, no restraint	7	2.4 ± 0.5	

\* Mean ± SEM.

<sup>a</sup> Compared to NS.

<sup>b</sup> Compared to GMBB + NS.

<sup>c</sup> Compared to GMBB + Ci.

In both trials II and III, administration of Tch and ASA significantly increased the incidence of stress-induced gastric lesions above that of the saline control groups. Furthermore, in the latter two trials, cimetidine reduced the number of erosions to a level not significantly different from the number of lesions produced by fasting and administration of a GMBB without cold restraint.

#### PRESENTATIONS

Levine BA: Cimetidine prevents stress-induced gastric erosions. Accepted for presentation, American College of Surgeons Surgical Forum, Dallas, TX, 20 October 1977.

#### PUBLICATIONS

Levine BA, Teegarden DK, McLeod CG Jr, Sirinek KR, Pruitt BA Jr: Cimetidine prevents stress-induced gastric erosions. Surg Forum 28:359, 1977.

Gastric erosions  
Cimetidine  
Rats

FINAL REPORT

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This study evaluated the effect of cimetidine, an H<sub>2</sub>-receptor antagonist, on gastric acid secretion in awake stressed and non-stressed rats with chronic gastric fistulae.

The findings were: (1) Cimetidine decreased total gastric acid output in stressed and non-stressed animals compared to controls; (2) Cimetidine decreased the acid concentration in the stomach of stressed and non-stressed animals compared to controls; (3) Control stressed rats demonstrated reduced total gastric acid output but unchanged acid concentration compared to non-stressed controls.

Conclusions were: (1) Acid concentration present in the stomach is more important than total acid output in formation of stress-related gastric mucosal injury; (2) Cimetidine's protective role in stress is related to its ability to decrease acid concentration in the stomach.

Gastric acid secretion  
Cimetidine  
Rats

GASTROINTESTINAL ALTERATIONS AND COMPLICATIONS IN BURNED TROOPS --  
STUDIES ON THE ETIOLOGY AND THERAPY OF STRESS ULCERS IN AN ANIMAL  
MODEL SIMULATING THE BURNED SOLDIER: B. EFFECT OF CIMETIDINE ON  
GASTRIC SECRETORY FUNCTION DURING STRESS

Stress has been shown to decrease gastric acid output in both animals and man (1-3). Despite this decrease, a sufficient amount of acid is present for gastric mucosal injury to occur. Since such injury requires this presence of acid to occur, investigators have pursued prophylactic treatment of this disease by utilizing methods to decrease gastric acidity (4,5).

With the advent of the  $H_2$ -receptor antagonist family of drugs, a new treatment modality has become available for use. The latest of these compounds, cimetidine (Smith Kline & French), has been shown to decrease gastric acid secretion in both basal and stimulated states. Previous experiments in our laboratory (6), as well as by others (7-10), have shown both cimetidine and metiamide

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10. Strauss RJ, Stein TS, Mandell C, Wise L: Prevention of stress ulcerations with cimetidine and carbenoxolone. *Surg Forum* 28:361, 1977.

Smith Kline & French) to decrease gastric mucosal injury related to restraint or hemorrhagic stress, either alone or in conjunction with gastric mucosal barrier breakers.

Few attempts have been made to correlate the protective effect of these drugs on gastric mucosa with their action on gastric acid output in the stress state. Those who have tried to do this have either been unsuccessful or have used inappropriate models for their studies (7,8). The purpose of these studies was to define the effect of the newest  $H_2$ -receptor antagonist, cimetidine, on gastric acid production in an awake model previously shown to produce acute, stress-related gastric mucosal injury.

#### MATERIALS AND METHODS

A total of 54 female C-D rats weighing 175 gm to 190 gm (Charles River Laboratories) were used for these experiments. All animals were prepared in the same manner. Intraperitoneal phenobarbital anesthesia was used. Stainless steel cannulae were placed through the squamous cell lined rumen of the stomach and secured in place with purse string sutures. These cannulae were then brought out through the left subcostal operative incision. All animals were then allowed to recover for at least seven days prior to study.

The rats were divided into two trial groups, stress and no stress, with each trial consisting of a control and a cimetidine-treated sub-group (Fig. 1). Each animal was fasted for 72 hours prior to the experiment, with water being allowed ad lib. At 48 hours of fasting, the stomachs were flushed and emptied of all particulate matter via the cannula.

In Trial I (no stress), there were 15 animals in each sub-group. Thirty minutes prior to the start of the experiment, each animal in the cimetidine sub-group received the drug in a dose of 20 mg/kg dissolved in saline as an intraperitoneal injection. The sub-group of control animals received 1 ml of normal saline in a like manner. Each rat was then placed in a separate cage and gastric secretions collected over four hours through an armored tube connected to the cannula.

In Trial II (stress), there were 12 control animals, while 11 animals received cimetidine. After both sub-groups received their respective intraperitoneal drug treatments (in the same doses as in Trial I), they were each placed in wire mesh restraints in a cold room at 4°C. Gastric secretions were collected through polyethylene tubing connected to the gastric cannula over a four-hour period.

# EXPERIMENTAL DESIGN

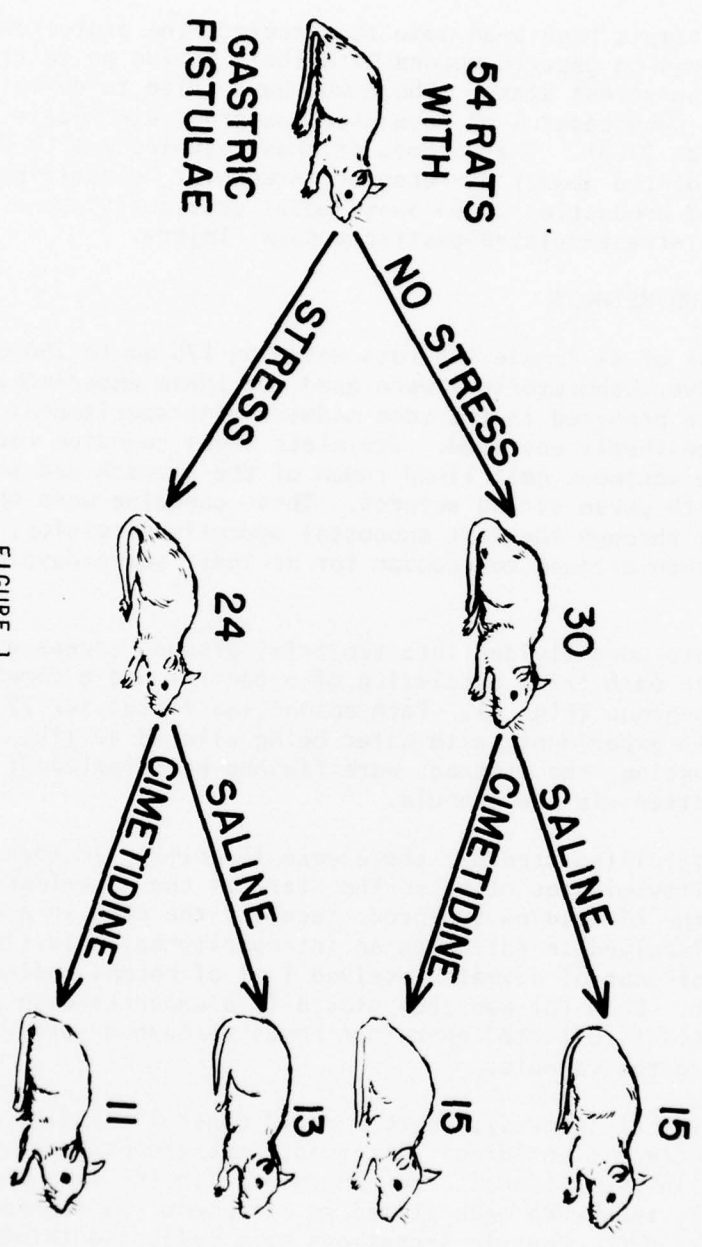


FIGURE 1



All gastric samples were filtered through coarse gauze to remove particulate matter. Volumes were recorded. Each animal's four-hour gastric output was then titrated to pH 7.0 with NaOH in an auto-burette (Radiometer). The acid concentration and total acid output were then calculated. Comparisons of the results between Trials I and II, as well as their sub-groups, were tested for statistical significance by the use of the Scheffé modification of Analysis of Variance.

## RESULTS

Cimetidine significantly reduced the mean volume of gastric juice in non-stressed rats, from  $0.72 \pm 0.07$  cc/hr in the controls to  $0.44 \pm 0.03$  cc/hr ( $p < .01$ ) (Fig. 2). There was no significant difference in gastric output volume between control ( $0.32 \pm 0.04$  cc/hr) and cimetidine-treated animals ( $0.42 \pm 0.04$  cc/hr) of the stress group. Furthermore, there were no significant volume differences between the non-stressed, cimetidine-treated rats and both sub-groups of Trial II.

Cimetidine significantly reduced acid concentration in the stomach in both stressed and non-stressed groups (Fig. 3). In the non-stressed animals, the acid concentration in the controls was  $63.38 \pm 3.68$  mEq/l versus  $50.80 \pm 3.90$  mEq/l for the cimetidine-treated animals ( $p < .05$ ). In the stress group, controls had an acid concentration of  $57.17 \pm 6.56$  mEq/l, while the concentration in cimetidine animals was  $17.29 \pm 1.94$  mEq/l ( $p < .01$ ). There was no significant concentration difference between the stressed and non-stressed controls. Finally, in the stressed animals, cimetidine caused an acid concentration decrease three times that seen in the unstressed trial.

Cimetidine also significantly reduced total acid output from that of controls in both trials (Fig. 4). In the non-stressed group, total acid output was  $47.22 \pm 6.39$   $\mu$ Eq/hr in the controls versus  $23.42 \pm 2.82$   $\mu$ Eq/hr in those treated with cimetidine ( $p < .01$ ). Stressed rats decreased their total output from  $18.54 \pm 3.41$   $\mu$ Eq/hr in controls to  $7.80 \pm 3.37$   $\mu$ Eq/hr in cimetidine-treated animals ( $p < .01$ ). Total acid output in the stressed control rats was significantly lower than in non-stressed controls ( $p < .01$ ) but unchanged from that seen in the unstressed cimetidine group ( $p = \text{NS}$ ).

## DISCUSSION

Decreased gastric acid secretion occurs secondary to several differing stresses. Skillman et al (3) have demonstrated a 72% reduction in acid secretion in normal males subjected to a rapid

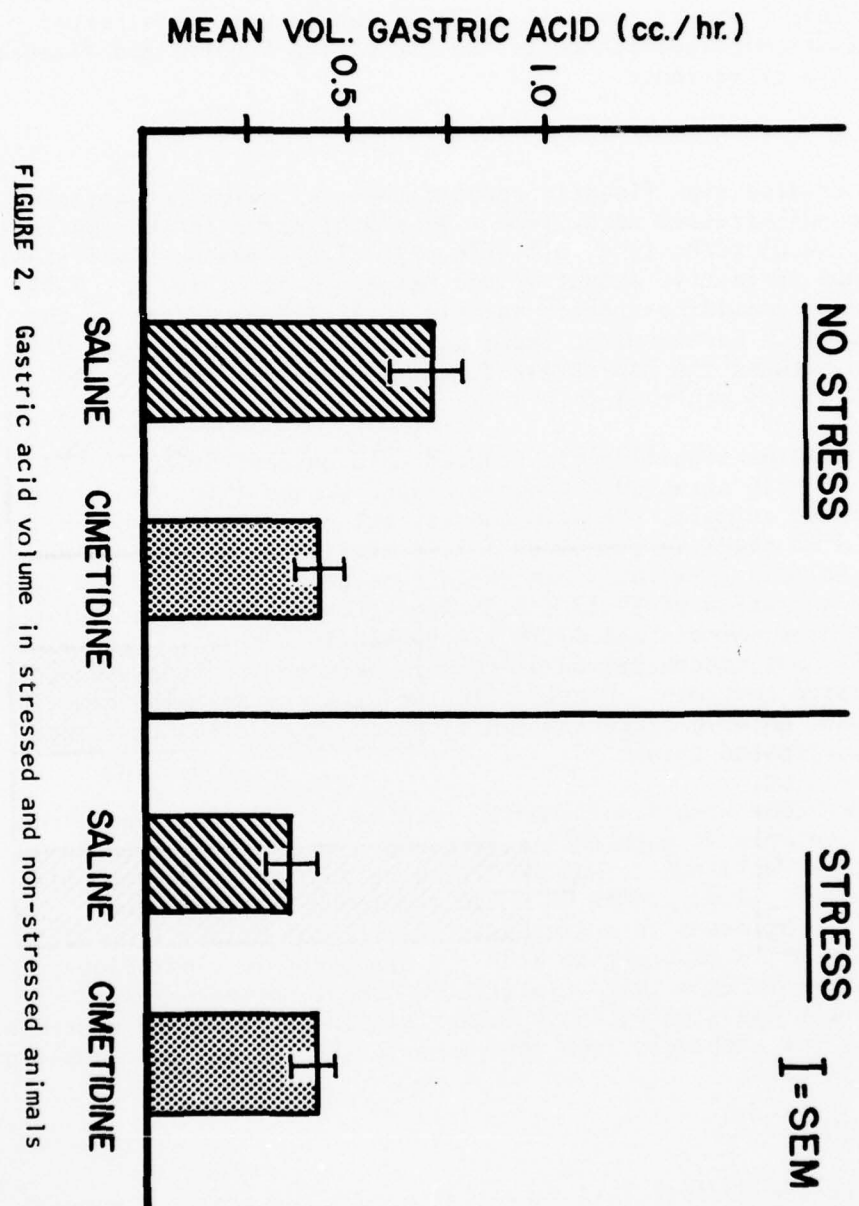


FIGURE 2. Gastric acid volume in stressed and non-stressed animals

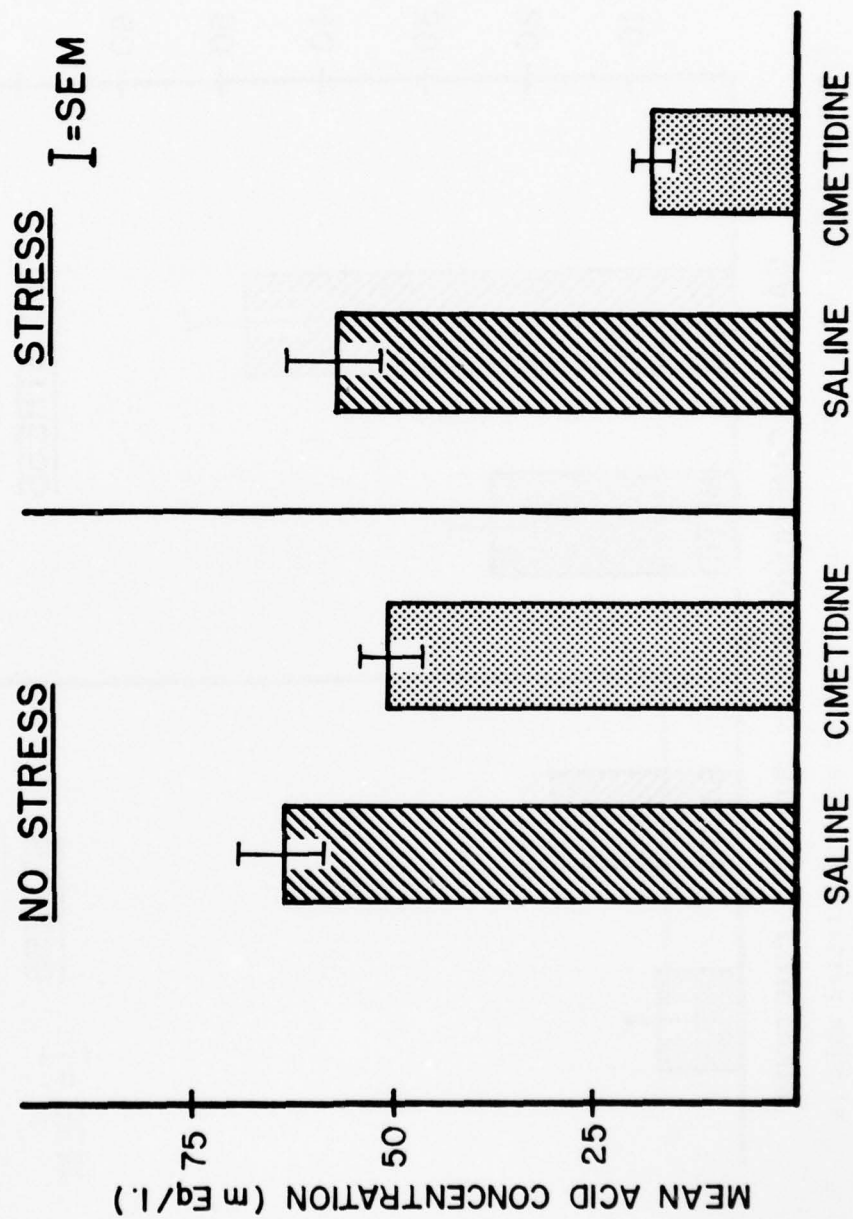


FIGURE 3. Gastric acid concentration in stressed and non-stressed animals

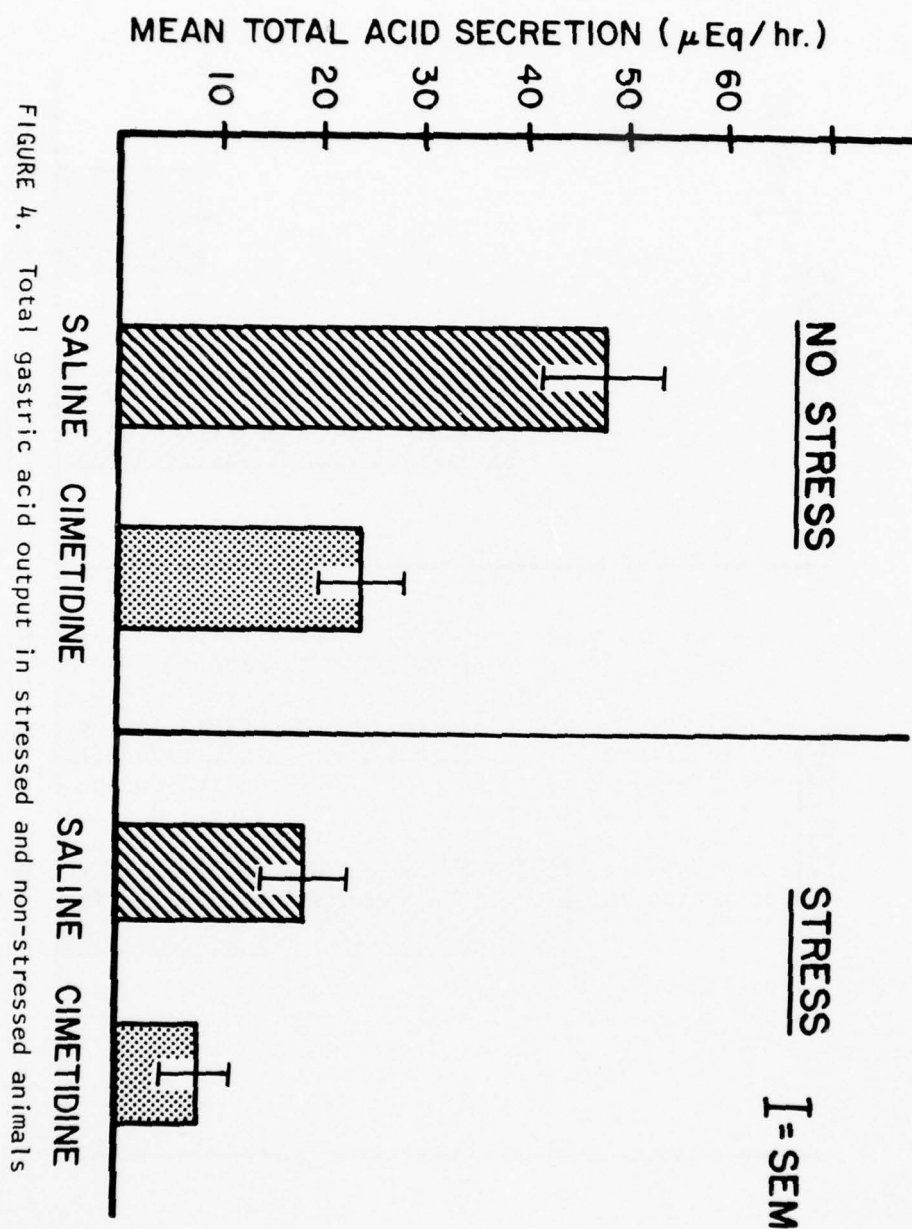


FIGURE 4. Total gastric acid output in stressed and non-stressed animals



hemorrhage of 15% of their blood volume. Similarly, Brodie and Moreno (1), as well as Dai and co-workers (8), have demonstrated decreases in volume of gastric secretions in restrained rats. However, at least in animal studies, this decrease has not prevented stress-related gastric mucosal injury. In fact, Mersereau and Hinchey (11) have utilized a hemorrhagically stressed rat model with an ex vivo gastric chamber to show that acid concentrations in the stomach as low as 25 mEq/l can still result in mucosal damage.

Several investigators have demonstrated the effectiveness of  $H_2$ -receptor antagonists in decreasing stress related gastric mucosal injury. However, those who have attempted to correlate this effect with their ability to lower acid have failed. Thus, Dai et al (8) found, in a cold-restraint, pylorus ligated rat model, that animals protected from gastric damage by metiamide had no lower acid output than controls. However, Brodie and Moreno (1) have shown that pylorus ligation in a rat is, by itself, a maximal stimulator of gastric acid secretion. Therefore, a model which utilizes this technique cannot yield results that are applicable to the human situation.

Bugajski and Danek (7) also used a cold-restraint rat model, but included a gastric fistula for acid collection. Of many metiamide dosages tried, only two, the smallest and the largest, afforded protection to the gastric mucosa. However, no correlation between this protection and gastric acid output could be made.

The model used for the experiments reported herein is the same one used at this Institute to show cimetidine's protective effect on gastric mucosa in the stressed rat (6). Neither the dosage of cimetidine, its route of administration, nor the type and size of animals used has been altered for these experiments. Therefore, the acid secretory data reported here can be extrapolated to those previously experimented animals with a known amount of gastric mucosal injury.

In the present study, cimetidine was capable of reducing total acid output by approximately 50% in stress and non-stress states. The effect of stress alone was enough to lower total acid to the level of that found in the cimetidine-treated, non-stressed rats. However, the acid concentration in the stressed control group was no lower than that of the non-stressed controls.

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Even though the total acid is decreased in this type of restraint model, a great deal of gastric damage can appear. Cimetidine has decreased such damage in this same model. In the present experiments, cimetidine lowered total acid output in the stress state without significantly decreasing the volume of gastric secretion. Instead, acid concentration was reduced by over 70% to 17.29 mEq/l. This figure is considerably below the minimum acid concentration determined by Mersereau (11) to be necessary for the gastric mucosa to ulcerate under stress. Thus, it would appear that cimetidine's role in protecting the stressed stomach depends on its ability to lower the concentration of intraluminal acid.

How this drug decreases acid concentration in the stomach during stress is open to speculation. It has been assumed that its major site of action is at the parietal cell  $H_2$ -receptor where it blocks the stimulatory effect of histamine. Investigators have been unable to demonstrate a consistent effect of  $H_2$  antagonists on gastric mucosal potential differences or hydrogen ion fluxes (9,10,12,13). However, Gurll et al (14) noted an increased  $H^+$  clearance from gastric pouches after metiamide administration. Could this effect be due to an altered mucosal blood flow allowing for more efficient disposal of acid-back diffusion? Evidence does exist for  $H_2$ -receptor mediation of vascular phenomena in the canine model (15,16). Further studies are necessary to delineate additional physiology in this area.

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#### PRESENTATIONS

Levine BA: Effect of cimetidine on gastric secretory function during stress. Accepted for presentation, Association for Academic Surgery, Seattle, Washington, November 1977.

#### PUBLICATIONS

Levine BA, Sirinek KR, Teegarden DK, McLeod CG, Pruitt BA: Effect of cimetidine on gastric secretory function during stress. Accepted for publication, Journal of Surgical Research.

PROGRESS REPORT

PROJECT NO. 3S1611102BS05-00, MILITARY BURN RESEARCH

REPORT TITLE: GASTROINTESTINAL ALTERATIONS AND COMPLICATIONS IN  
BURNED TROOPS -- ULCERATIVE GASTRIC DISEASE IN THE  
SEPTIC BURNED RAT: A MODEL FOR THE STUDY OF NON-  
HEALING STRESS ULCERS IN THE MILITARY POPULATION

US ARMY INSTITUTE OF SURGICAL RESEARCH  
BROOKE ARMY MEDICAL CENTER  
FORT SAM HOUSTON, TEXAS 78234

1 October 1976 - 30 September 1977

Investigators:

Charles G. McLeod, Jr., Major, VC  
Albert T. McManus, Captain, MSC  
Thomas W. Panke, M.D., Major, MC  
Arthur D. Mason, Jr., M.D.

Reports Control Symbol MEDDH-288(R1)

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ANNUAL RESEARCH PROGRESS REPORT, 1 OCTOBER 1976-30 SEPTEMBER 19--ETC(U)  
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ABSTRACT

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In animal studies at the Institute of Surgical Research, erosive and ulcerative gastric mucosal lesions appear sporadically in laboratory animals subjected to various experimental procedures. Very mild erosive lesions are seen in animals after experimental burns or other forms of stress. Deeper erosive and ulcerative gastric mucosal lesions are found most frequently in animals that are experimentally or spontaneously infected with gram-negative bacteria. It has been observed that gram-negative bacteria are present in some of the gastric lesions of septic animals, whereas none are usually seen in lesions of nonseptic animals. Additionally, a necrotic bacterial vasculitis typical of that described in the skin of animals and man with invasive *Pseudomonas* infection has been seen in submucosal vessels of the stomach of septic animals. These lesions occur at a very low frequency in the animals studied thus far.

Studies were begun in late summer to determine the incidence and histopathology of gastric erosions and ulcerations in the septic burned rat. These preliminary experimentations with burned *Pseudomonas aeruginosa* infected rats and burned uninfected rats have revealed that, when the burn size is 30%, gastric erosions and ulcerations appear only in the rats which have sepsis. Also, it has been found that restriction of food intake increases the incidence of gross lesions in the gastric mucosa of both septic and nonseptic burned rats. Microscopic examination of tissues has not been completed. However, in future studies the incidence and significance of gram-negative bacteria in the gastric lesions will be determined.

Burn injury

Infection

Gastric ulcers

PROGRESS REPORT

PROJECT NO. 3S1611102BS05-00, MILITARY BURN RESEARCH

PROJECT TITLE: GASTROINTESTINAL ALTERATIONS AND COMPLICATIONS IN  
BURNED TROOPS -- EFFECT OF H<sub>2</sub> ANTAGONISM ON GASTRIC  
BLOOD FLOW DISTRIBUTION IN THE STRESSED PIGLET

US ARMY INSTITUTE OF SURGICAL RESEARCH  
BROOKE ARMY MEDICAL CENTER  
FORT SAM HOUSTON, TEXAS 78234

1 October 1976 - 30 September 1977

Investigators:

Barry A. Levine, M.D., Major, MC  
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Basil A. Pruitt, Jr., M.D., Colonel, MC

\*Univ of Texas School of Medicine, San Antonio

Report Control Symbol MEDDH-288(R1)

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# ABSTRACT

PROJECT NO. 3S1611102BS05-00, MILITARY BURN RESEARCH

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The therapeutic capacity of cimetidine to reduce gastric mucosal injury is thought to be secondary to its ability to block gastric acid secretion. This study evaluates cimetidine's possible vascular role in regulating gastric mucosal blood flow in the stressed pig.

Eleven piglets (9-12 kg) were anesthetized (chloralose 100 mg/kg), intubated, and ventilated. Catheters placed in both femoral arteries and veins allowed monitoring of systemic arterial pressure, CVP, pulmonary arterial pressure, and determination of cardiac output (thermal dilution). A left ventricular catheter allowed injection of up to four separate doses of radioactive microspheres (<sup>125</sup>I, <sup>141</sup>CE, <sup>85</sup>SR, <sup>46</sup>SC) to measure gastric blood flow. Following 30 min of stabilization, hemorrhagic shock (50 mmHg) was induced and maintained for 90 min in all 11 pigs. Four of these pigs received cimetidine (10 mg/kg IV) prior to shock. Gastric blood flow measurements were made 30 min after stabilization, 30 min after cimetidine injection (pre-shock) and after 90 min of shock.

At 90 min of shock, identical reductions (+60%) in mean arterial pressure and cardiac output occurred in both treatment groups. In control animals, significant reductions in gastric mucosal blood flow occurred with shock (Table 1). In cimetidine-treated animals, gastric mucosal blood flow either after cimetidine (pre-shock) or after 90 min of shock was not significantly different from baseline values.



Table 1. Gastric Mucosal Blood Flow (ml/min/100 gm tissue)

	CONTROL		CIMETIDINE		
	Baseline	90' Shock	Pre-Shock Baseline	Post-Cim.	90' Shock
Fundus	14.0±1.6	5.8±1.6*	18.3±4.1	20.7±3.3**	14.7±1.5**
Corpus	16.3±1.2	7.6±1.9*	19.3±1.7	24.0±3.8**	16.5±1.8**
Antrum	16.0±0.8	6.8±2.0*	20.5±3.5	21.9±1.8**	14.5±1.1**

\* P < 0.05 compared to baseline; \*\* P = NS compared to baseline; Scheffé modification of Analysis of Variance was used to make all statistical comparisons

These results clearly demonstrate the capacity of pre-shock cimetidine to protect against significant reductions in gastric mucosal blood flow, suggesting an additional mechanism by which prophylactic cimetidine protects against gastric mucosal injury.

Cimetidine  
Piglets  
Blood flow

RESEARCH AND TECHNOLOGY WORK UNIT SUMMARY				1. AGENCY ACCESSION <sup>a</sup>	2. DATE OF SUMMARY <sup>a</sup>	REPORT CONTROL SYMBOL	
				DA OG 6974	77 10 01	DD-DR&E(AR)636	
3. DATE PREV. SUMM <sup>a</sup>	4. KIND OF SUMMARY	5. SUMMARY SCTY <sup>a</sup>	6. WORK SECURITY <sup>a</sup>	7. REGRADING <sup>a</sup>	8. DISSEM INSTR <sup>a</sup>	9. SPECIFIC DATA - CONTRACTOR ACCESS	10. LEVEL OF SUM
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11. NO. / CODES <sup>a</sup>		PROGRAM ELEMENT	PROJECT NUMBER	TASK AREA NUMBER	WORK UNIT NUMBER		
A. PRIMARY		61102A	3S 1611102BS05	00	084		
B. CONTRIBUTING							
C. CONTRIBUTING							
11. TITLE (Precede with Security Classification Code) <sup>a</sup>							
(U) Alterations in Pulmonary Function and Pulmonary Complications in Burned Soldiers (44)							
12. SCIENTIFIC AND TECHNOLOGICAL AREAS <sup>a</sup>							
003500 Clinical Medicine							
13. START DATE		14. ESTIMATED COMPLETION DATE		15. FUNDING AGENCY		16. PERFORMANCE METHOD	
76 10		Cont		DA		C. In-House	
17. CONTRACT GRANT				18. RESOURCES ESTIMATE			
Not Applicable				PRECEDING			
A. DATES/EFFECTIVE:				B. PROFESSIONAL MAN YRS			
D. NUMBER <sup>a</sup>				FISCAL			
C. TYPE				YEAR			
E. KIND OF AWARD				CURRENT			
F. CUM. AMT.				77 1.9 30			
78 2.1 50							
19. RESPONSIBLE DOD ORGANIZATION				20. PERFORMING ORGANIZATION			
NAME <sup>a</sup> US Army Institute of Surgical Research				NAME <sup>a</sup> US Army Institute of Surgical Research			
ADDRESS <sup>a</sup> Ft Sam Houston, Tx 78234				ADDRESS <sup>a</sup> Ft Sam Houston, Tx 78234			
RESPONSIBLE INDIVIDUAL				PRINCIPAL INVESTIGATOR (Furnish SSAN if U.S. Academic Institution)			
NAME: Basil A Pruitt, Jr, COL, MC				NAME <sup>a</sup> Victor Lam, MAJ, MC			
TELEPHONE: 512-221-2720				TELEPHONE: 512-221-6532			
21. GENERAL USE				SOCIAL SECURITY ACCOUNT NUMBER:			
FOREIGN INTELLIGENCE NOT CONSIDERED				ASSOCIATE INVESTIGATORS			
				NAME:			
				NAME:			
				DA			
22. KEYWORDS (Precede EACH with Security Classification Code)							
(U) Burn injury; (U) Pulmonary function tests; (U) Bronchoscopy; (U) Humans; (U) Goats;							
(U) Pulmonary extravascular water; (U) Total thoracic resistance							
23. TECHNICAL OBJECTIVE <sup>a</sup> 24. APPROACH 25. PROGRESS (Furnish individual paragraphs identified by number. Precede text of each with Security Classification Code.)							
23. (U) To document the site of inhalation injury early in the clinical course and to follow its progression quantitatively. To develop a goat model of inhalation injury with plastic polymers (toluene di-isocyanate) as the agent of injury.							
24. (U) Total respiratory system will be measured by the oscillometrics method. Polyurethane foam will be ignited to produce inhalation injury in tracheostomized goats. Serial measurements of pulmonary function and pathologic studies will be obtained.							
25. (U) 76 10 - 77 09 Two patients have been studied to date. Oscillometrics apparatus is operational, with 5% to 10% standard deviation in measurements with 6 normals. A trial of on-line computer analysis of oscillometrics data has been accomplished. Analysis of smoke sample and post-mortem lung section by gas chromatography for isocyanates, acetaldehyde and carbon monoxide is being evaluated to standardize dose-injury relationship in the goat model of inhalation injury.							

<sup>a</sup>Available to contractors upon originator's approval.

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1 MAR 66

PREVIOUS EDITIONS OF THIS FORM ARE OBSOLETE. DD FORMS 1498A, 1 NOV 68 AND 1498-1, 1 MAR 66 (FOR ARMY USE) ARE OBSOLETE.

PROGRESS REPORT

PROJECT NO. 3S1611102BS05-00, MILITARY BURN RESEARCH

REPORT TITLE: ALTERATIONS IN PULMONARY FUNCTION AND PULMONARY  
COMPLICATIONS IN BURNED SOLDIERS -- EVALUATION OF  
UPPER AIRWAY OBSTRUCTION IN THERMAL INJURY BY FORCED  
OSCILLATIONS

US ARMY INSTITUTE OF SURGICAL RESEARCH  
BROOKE ARMY MEDICAL CENTER  
FORT SAM HOUSTON, TEXAS 78234

1 October 1976 - 30 September 1977

Investigators:

Victor Lam, M.D., Major, MC  
Cleon W. Goodwin, Jr., M.D., Major, MC  
E. W. Hander, M.A.  
Douglas W. Mills, Second Lieutenant, MSC  
SP5 Keith D. Johns

Reports Control Symbol MEDDH-288(R1)

UNCLASSIFIED

# ABSTRACT

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Inhalation injury has been implicated as an etiology for increased mortality from thermal injury. Upper airway obstruction has been previously assessed qualitatively by bronchoscopy or auscultation.

This study will measure total thoracic resistance by the effort-independent forced oscillation method. Computer interfacing details remain to be accomplished.

Burn injury  
Pulmonary function tests  
Total thoracic resistance  
Upper airway obstruction



ALTERATIONS IN PULMONARY FUNCTION AND PULMONARY COMPLICATIONS IN  
BURNED SOLDIERS -- EVALUATION OF UPPER AIRWAY OBSTRUCTION IN  
THERMAL INJURY BY FORCED OSCILLATIONS

Inhalation injury is a common feature of burned patients. However, clinical findings and history, such as singed nasal vibrissae, carbonaceous sputum, facial burn, or closed space fires, are not reliable indicators of inhalation injury.

Currently, fiberoptic bronchoscopy and xenon perfusion lung scans are the most accurate methods for the diagnosis of upper airway injury and obstruction, but they are not practical for serial measurements.

Measurement of total respiratory system resistance by forced oscillations will allow repetitive, non-invasive, effort-independent measurements to document the degree of airway injury or obstruction (1). By determination of frequency characteristics of resistance, the site of airway involvement can be ascertained. Therapeutic intervention can be quantitated for time course, effect, and site of action.

#### METHODS AND MATERIALS

Respiratory resistance is measured by the superimposition of pressure oscillations on the subject's breathing pattern through flexible tubing attached to a loudspeaker driven by a sine wave function generator at 5 and 11 hertz. A bias flow is maintained by a blower (Collins) at .5 liters/sec in order to prevent build-up of carbon dioxide in the apparatus.

Flow is measured at the mouth with a screen pneumotachygraph (Electronics for Medicine) connected to a Validyne MP45 transducer. The system is dynamically balanced to a frequency of 15 hertz. There is a constant 60° phase angle shift between the pneumotachygraph and mouth pressure transducer, which is compensated for prior to data computation.

The mouth pressure, flow, and volume signal are entered via analog to digital converters into the DEC computer system. A computer program allows for the recording of baseline and calibration levels for all three signals. During the procedure, flow, pressure and volume are converted to digital data and recorded at .01 second intervals for 10.24 seconds. A fast fourier transform is performed

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1. Baier H, Wanner A, Zarzecki S, Sackner MA: Relationships among glottis opening, respiratory flow, and upper airway resistance in humans. J Appl Physiol 43:603-611, 1977.

on the flow signal, and its power spectrum is computed. The power spectrum is analyzed for peaks greater than 2% of the total power. Only recordings containing one peak are retained.

After a fast fourier transform is performed for the pressure signal, the amplitude and phase angle between the pressure and flow data are retained for computation of pulmonary resistance.

The seated subject breathes via a mouthpiece. A volume history is obtained, and duplicate measurements are obtained at 5 and 11 hertz.

#### PROGRESS

Initial studies with normal subjects on forced oscillation apparatus yielded resistance measurements with a coefficient of variation of 6%. This was obtained with breath-by-breath analysis via data entry on the Hewlett-Packard 9830A digitizer system. However, the technician time required to enter the recordings of pressure, flow and volume was excessive.

The current forced oscillation apparatus is unable to generate the required 0.5 liter/second flows in the thermally injured patients. We are awaiting the implementation of a larger 24" transducer and sine wave function generator.

In order to perfect the technique for obtaining respiratory resistance, we have measured resistance change during antigen skin testing in extrinsic asthmatics. The method appears able to differentiate allergic rhinitis patients from those with extrinsic asthma by skin testing.

Further progress is expected when breath-by-breath analysis with corrections for lung volumes and tidal breathing will allow reduction in the coefficient of variation.

#### PRESENTATIONS AND/OR PUBLICATIONS

None.

TERMINATION

PROJECT NO. 3S1611102BS05, MILITARY BURN RESEARCH

PROJECT TITLE: ALTERATIONS IN PULMONARY FUNCTION AND PULMONARY COMPLICATIONS IN BURNED SOLDIERS-AEROSOLIZED GENTAMICIN IN THE PROPHYLACTIC TREATMENT OF INHALATION INJURY

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C. Lawrence Slade, M.D., Captain, MC  
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Reports Control Symbol MEDDH-288 (RI)

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## ABSTRACT

PROJECT NO. 3S1611102BS05, MILITARY BURN RESEARCH

REPORT TITLE: ALTERATIONS IN PULMONARY FUNCTION AND PULMONARY COMPLICATIONS IN BURNED SOLDIERS-AEROSOLIZED GENTAMICIN IN THE PROPHYLACTIC TREATMENT OF INHALATION INJURY

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Reports Control Symbol MEDDH-288 (RI)

The addition of an inhalation injury to a cutaneous burn results in a significant increase in patient mortality rates, both from early pulmonary edema and later, gram negative pneumonitis. Steroids have been shown to decrease mortality in an inhalation injury model. Aerosolization of gentamicin has been used successfully to treat severe bronchial infections. Therefore, a prospective, randomized trial was undertaken to evaluate both these drugs.

Sixty burned patients, with inhalation injury confirmed by bronchoscopy and <sup>133</sup>Xenon scan, were studied. Thirty patients received either dexamethasone or saline placebo for three days. Serial pulmonary functions were measured on those able to cooperate. Another 30 patients received either aerosolized gentamicin or placebo for ten days.

Both drug treated groups were comparable to their controls in age and mean burn size. Results of the steroid trial showed no major differences in mortality, pulmonary complications, or changes in pulmonary functions. Results of the gentamicin trial showed no major differences in mortality, time of death, or pulmonary and septic complications between treated and control groups.



## ALTERATIONS IN PULMONARY FUNCTION AND PULMONARY COMPLICATIONS IN BURNED SOLDIERS-AEROSOLIZED GENTAMICIN IN THE PROPHYLACTIC TREATMENT OF INHALATION INJURY

Inhalation injury in conjunction with cutaneous burns is associated with an exceedingly high mortality rate. Surveys of thermally injured patients by Achauer (1), Stone (2), and at our own institution, reveal an incidence of pulmonary injury secondary to the inhalation of noxious products of combustion in 15-22% of all admissions. The mortality rate for this combined injury ranged from 48-86%. More importantly, as Agee (3) and his colleagues observed, the actual mortality rate of a group of patients with both injuries far exceeds the expected mortality rate for that group if only cutaneous thermal injury was present.

Pathophysiologic studies of inhalation injury show evidence of an early increase in lung water, congestion, and inflammation. Stephenson (4) and co-workers have shown that these alterations in the lung parenchyma lead to a decreased compliance, and a increased alveolar-arterial  $pO_2$  gradient due to shunting, hypoxia, and increased pulmonary vascular resistance. In addition, airway flow is decreased and resistance is increased (5). Physiologic alterations are not limited to the lung. Cardiac output and blood pressure are decreased, while systemic resistance is increased.

Steroids have been recommended in the early treatment of inhalation injury in an attempt to decrease the inflammatory and edematous pulmonary changes (6). Although some laboratory data exists supporting this recommendation, no controlled human studies have been attempted. The first

- 
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  2. Stone HH, Martin JD: Pulmonary injury associated with thermal burns. *SGO* 129: 1242-1246, 1969.
  3. Agee RN, Long JM, Hunt JL, et al: Use of  $^{133}\text{Xe}$  in early diagnosis of inhalation injury. *J Trauma* 16: 218-224, 1976.
  4. Stephenson SF, Esrig BC, Polk HC, et al: The pathophysiology of smoke inhalation injury. *Ann Surg* 182: 652-660, 1975.
  5. Petroff PA, Hander EW, Clayton WH, et al: Pulmonary function studies after smoke inhalation. *Am J Surg* 132: 346-351, 1976.
  6. Phillips AW, Cope O: Burn therapy II. The revelation of respiratory tract damage as a principal killer of the burned patient. *Ann Surg* 155: 1-8, 1962.

portion of this trial evaluated the efficacy of short term parenteral steroids in patients with both an inhalation injury and a cutaneous burn.

A majority of the morbidity and mortality associated with inhalation injury is due to bacterial, especially gram negative, pneumonias 1,7,2. Aerosolized prophylactic antibiotics have been used successfully in other clinical settings (8,9,10). Thus, the second portion of this trial investigated the value of prophylactic aerosolized gentamicin in the treatment of patients with combined inhalation and thermal cutaneous injuries.

#### Methods & Materials

All thermally injured patients, 16 years of age or older suspected of inhalation injury and admitted within 72 hours of that injury, were used as the basis of these studies (Table I). Each of the 60 patients in this group underwent flexible fiberoptic bronchoscopy on admission. Fifty-four of these patients also underwent  $^{133}\text{Xe}$  lung scans within 24 hours of admission. Only those patients with positive bronchoscopic findings of carbonaceous material or of tracheobronchial mucosal edema, erythema, hemorrhage, or ulceration were included in the study. A negative  $^{133}\text{Xe}$  scan (complete washout of the intravenously injected  $^{133}\text{Xe}$  dose within 90 seconds) did not eliminate a patient from the study if the bronchoscopic examination was positive.

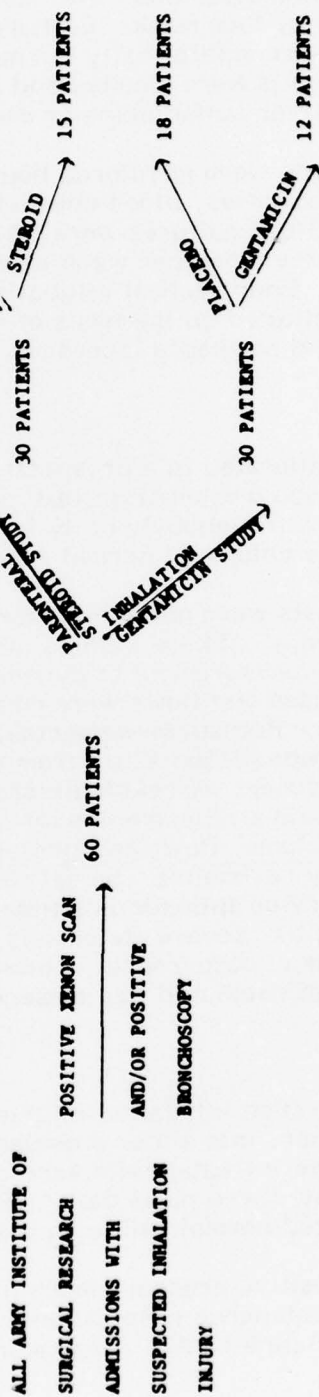
The patient groups used in each of the drug trials were mutually exclusive. Therefore, no patient was entered into both the gentamicin and the steroid trial groups. The studies were explained fully to each patient or his next of kin. An informed consent was obtained prior to entry into the study.

- 
7. DiVincenti FC, Pruitt BA, Beckler JM: Inhalation injuries. *J Trauma* 11: 109-116, 1971.
  8. Greenfield S, Teres D, Bushnell LS, et al: Prevention of gram negative bacillary pneumonia using aerosol polymyxin as prophylaxis. *J Clin Invest* 52: 2935-2940, 1973.
  9. Klatersky J, Geuning C, Mouawad E, et al: Endotracheal gentamicin in bronchial infections in patients with tracheostomy. *Chest* 61: 117-120, 1972.
  10. Klatersky J, Hensgens C, Noterman J, et al: Endotracheal antibiotics for the prevention of tracheobronchial infections in tracheotomized unconscious patients. *Chest* 68: 302-306, 1975.

TABLE I

Inhalation Injuries

OUTLINE FOR INHALATION INJURY STUDY



All patients in both trials were resuscitated over the first 24 hours with Ringer's lactate solution in amounts sufficient to maintain a urine output of at least 50 milliliters per hour with stable vital signs. Humidified oxygen was given by face mask. Escharotomies were performed only as necessary on all circumferentially burned extremities as well as the thorax. All burn wounds were cleaned and debrided upon admission and treated with either silver sulfadiazine or mafenide acetate creams.

The patient's vital signs were monitored hourly for at least the first three days. Arterial blood gases, blood chemistries, and CBC's were obtained at least daily. Blood cultures were taken from antiseptically prepared sites at least three times per week as well as during any presumed episode of sepsis. Endotracheal intubation with controlled mechanical ventilation was instituted on the basis of recognized criteria of hypoxia, hypercarbia, and markedly increased respiratory rate.

#### Steroid Group

Thirty patients were allocated in a prospective, randomized manner into either the steroid or placebo treatment groups. Fifteen patients received 20 mgs of dexamethasone intravenously daily for three days while another 15 patients received a like volume of normal saline on a similar schedule.

Pulmonary function tests were obtained prior to the initial treatment and after 48 hours of therapy. These studies included maximum expiratory flow - volume curves and measurement of dynamic compliance and pulmonary resistance. Volumes and flows were measured using an Ohio model 840 dry spirometer. Pressures were obtained with a 12 cm esophageal balloon, the tip of which was placed 42 cm from the nares and connected to a Statham pressure transducer. A Tektronix oscilloscope was employed for recording the MEFV, and an Electronics for Medicine strip recorder was used for recording volume, flow, and pressure signals for the dynamic compliance and pulmonary resistance. Serial electrocardiograms and X-rays were reviewed. Pulmonary complications attributable to inhalation injury (e.g. pneumonitis, bronchitis, severe atelectasis, and lobar collapse) were noted along with their time of occurrence. Finally, pathology reports were reviewed as to the cause of death and the presence of pulmonary lesions.

#### Gentamicin Group

Thirty patients with proven inhalation injuries were allocated in a prospective, randomized manner, into either a gentamicin or a placebo treated group. Twelve patients were treated with aerosolized gentamicin, 80 mg in two milliliters of diluent, three times daily. Eighteen patients received two milliliters of aerosolized normal saline on the same schedule.

A Byrd intermittent positive pressure machine was used to deliver the drugs in patients with spontaneous respiration. In patients requiring ventilatory assistance, a Bennett MA-1 respirator was employed for drug



administration. Both of these machines were fitted with a Bard-Parker U-Med moduflex nebulizer which delivers 89.4% of the emitted particles in the range of 1.0-1.8 micra in diameter.

Therapy continued for 10 days. Lukens tube cultures were taken prior to inhalation of therapy and on alternate days thereafter. These were examined for predominant organisms with quantitative counts of those organisms being obtained. The chest roentgenograms were taken daily for at least the first ten days and twice weekly thereafter. No attempt was made to control parenteral antibiotic administration by the primary physicians. At the close of the study the two subgroups were compared for survival, sepsis, bacteriology, respiratory complications and autopsy findings.

The drug treated groups in both trials were compared for statistical significance to their controls by the Normal Difference Test.

### Results

Control and treated groups in both trials were similar in both age and mean percent body surface burn. (Table II). In the gentamicin trial, although the mean burn size of both saline and antibiotic treated patients was similar, half of the saline controls had burns over greater than 60% of their body surface (Table III). In contrast, the gentamicin treated group contained only two patients with such severe injuries. Most patients in this latter group had suffered 40-60% total body surface burns.

### Steroid Trial

Sixty percent of the patients receiving parenteral dexamethasone died, 20% of them within ten days of injury (Table IV). This compared with a 73.3% total mortality rate for the placebo group with an identical 20% mortality within the first ten days post-injury. The rates of pulmonary complications for the dexamethasone and placebo patients were 73.3% and 86.7% respectively. In the steroid treated patients 26.7% died as a direct result of pulmonary complications; whereas 46.7% of the control group did so.

Seven of the steroid treated patients and five controls were able to undergo pulmonary function measurements prior to and after 48 hours of treatment (Table V). Both groups showed a slight decrease in vital capacity and peak flow with little change in flow rates at 50% and 25% of vital capacity. Pulmonary resistance decreased in the steroid treated group. Unfortunately, no 48 hour pulmonary resistance measurements could be made in any of the controls; so comparisons could not be made. The differences in pulmonary functions, mortality, and morbidity between the two groups were not significant.

TABLE II

## Inhalation Injuries

		<u>PATIENT DATA</u>	
	<u>#</u>	<u>MEAN AGE (YRS)</u>	<u>MEAN PERCENT TBS* BURN</u>
<u>Steroid Trial</u>			
Placebo	15	29.7	56.0
Dexamethasone	15	33.3	51.2
<u>Gentamicin Trial</u>			
Placebo	18	28.1	57.6
Gentamicin	12	34.3	53.8

\*TBS = Total Body Surface

TABLE III

Inhalation Injuries

PATIENT BURN SIZE DATA IN GENTAMICIN TRIAL

BURN SIZE (TBS)

	<u>&lt;40%</u>	<u>40-60%</u>	<u>&gt;60%</u>
Placebo Patients	5	4	9
Gentamicin Patients	1	9	2

TABLE IV

## Inhalation Injuries

STEROID TRIAL RESULTS

	#	%MORTALITY (TOTAL)	%MORTALITY 1st 10 DAYS)	%PULMONARY COMPLICATIONS	% DYING OF PULMONARY COMPLICATIONS
Placebo Patients	15	73.3	20.0	86.7	46.7
Dexamethasone Patients	15	60.0	20.0	73.3	26.7



TABLE V

## Inhalation Injuries

STEROID TRIAL - PULMONARY FUNCTION DATA

#	Vital Capacity (L.)		Peak Flow (L/Sec)		Flow at 50% VC (L/Sec)		Flow at 25% VC (L/Sec)		Pulmonary Resistance		
	0 hr	48 hr	0 hr	48 hr	0 hr	48 hr	0 hr	48 hr	0 hr	48 hr	
Placebo Patients	5	4.50	4.24	8.62	8.49	5.10	5.30	2.12	2.13	-	-
Dexamethasone Patients	7	4.08	3.65	6.45	6.25	2.85	2.84	1.09	1.23	4.64	3.76

### Gentamicin Trial

There was a 50% overall mortality rate in the gentamicin treated patients with an average time to death of 9.3 days. The mortality rate in the placebo group was 66.7% with an average time to death of 8.6 days. As noted earlier, there were many more patients with larger burns (greater than 60% total body surface) in the placebo group. Patients with burns of this size have a poor prognosis even without the addition of other serious injuries. Thus, the mortality rates of the two groups were compared further using only those patients with burns of less than 60% total body surface. The mortality rate for the gentamicin group was then 40% and that of the placebo group was 44.4%.

Patients in both groups had high rates of pulmonary complications. In the gentamicin group 66.7% of patients had X-ray evidence of pulmonary infiltrate, 58.3% required mechanical ventilation, and 66.7% died of significant pulmonary complications. In those patients receiving placebo 66.7% had pulmonary infiltrates, 66.7% required mechanical ventilation, and 83.3% died as a result of pulmonary complications.

The time to either development of a pulmonary infiltrate or to endotracheal intubation did not differ in the two groups. The first pulmonary infiltrate appeared at 5.5 days post-burn in the controls and at 6.4 days post-burn in the gentamicin group. The average post-burn time of intubation for the 12 affected control patients was 4.5 days, and that of the seven gentamicin treated patients was 5.4 days. Seventy-five percent of both the treated and control groups had sputum cultures in which Pseudomonas aeruginosa was the predominant organism.

Sepsis played a major role in both groups of patients. Seventy-five percent of the gentamicin group and 72.2% of controls had blood culture proven sepsis during their course. The overwhelming type of sepsis was gram negative with the predominant organisms being Pseudomonas Aeruginosa and Klebsiella pneumoniae in both groups. The first positive blood culture in both the control and gentamicin groups occurred on the sixth post-burn day.

As in the steroid trial, all comparisons between the gentamicin and placebo groups failed to reach statistical significance.

### Discussion

Average burn size for all of the 60 patients in this series (54.8% total body surface) was similar to that in Achauer's study (1). Overall mortality (63.3%) and pulmonary complication (73.3%) rates for this series were comparable to others reviewed. (1,2) Use of both <sup>133</sup>Xenon scan and fiberoptic bronchoscopy assured that only patients with genuine inhalation injuries were included in the study.

The use of steroids in inhalation injury has been suggested to decrease the early inflammatory and edematous pulmonary changes. Dressler (11) utilized a rat model exposed to white pine smoke to test this hypothesis. Of four corticosteroid analogues used, only methylprednisolone and dexamethasone were effective. Each of these drugs reduced mortality rates by at least 75%. The reduced mortality in the steroid treated animals was also correlated with a decrease in the interstitial edema, atelectasis, and inflammatory changes compared to the controls.

Although the acute pulmonary injury associated with smoke inhalation can be altered favorably with steroids, these drugs carry deleterious consequences as well. The effect of short term steroid therapy on pulmonary bacterial clearance was studied in rats by Skornik and Dressler. (12) They found that all corticosteroid preparations used caused a decrease in bacterial clearance by the lung, with dexamethasone having the greatest effect. Addition of a clean 20% cutaneous burn wound further decreased the clearance in the steroid treated animals. Seeding of the cutaneous burn with Pseudomonas aeruginosa decreased clearance still further. Mortality rates in the various groups were inversely proportional to the bacterial clearance rates.

Thus, it is evident, that if a beneficial therapeutic effect is to be seen with steroids and inhalation injury, they should be used early enough to affect physiologic changes in the lung favorably and withdrawn before the bacteria on the burn wound can seed the tracheobronchial tree. For this reason steroids in the current trial were given for only the initial three days of treatment.

Despite the theoretical and experimental advantages claimed for steroids, no striking differences were evident between control and dexamethasone treated patients in mortality, morbidity, or pulmonary function changes. This lack of effect may be due to two causes. First, all patients had rather large burns and consequently, generous amounts of resuscitative fluids were administered. This may have placed an amount of fluid in the lung parenchyma which could not be affected by the steroids given.

Secondly, the large, average burn size yielded a fertile field, even with topical antibiotics, for bacterial growth. Three days of steroid treatment may have been enough to lower host defenses to allow for even more rapid

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11. Dressler DP, Skornik WA, Kupersmith S: Corticosteroid treatment of experimental smoke inhalation. *Ann Surg* 183: 46-52, 1976.
  12. Skornik WA, Dressler DP: The effects of short-term steroid therapy on lung bacterial clearance and survival in rats. *Ann Surg* 179: 415-421, 1974.

bacterial seeding of the lungs. This, coupled with decreased lung bacterial clearance, could account for the high pulmonary complication rate in the dexamethasone group.

After the acute phase of inhalation injury is over, most morbidity and mortality referable to the injury is secondary to bacterial pneumonitis (1,7,2). Esrig (13) and colleagues demonstrated this in a canine smoke inhalation model. The animals who received an inhalation injury plus an intratracheal pseudomonas inoculation, had a significantly higher mortality than control dogs with either an inhalation injury or pseudomonas inoculation alone.

The use of prophylactic antibiotics as aerosols in order to prevent gram negative pneumonias, has been evaluated recently by several groups. Berendt (14) has shown that aerosolized kanamycin worked better than intramuscular doses in treating *Klebsiella pneumoniae* pulmonary infections in mice. Klatersky (9,10) and co-workers have demonstrated that aerosolized gentamicin, as compared with intramuscular dosage, yields higher drug concentrations in bronchial secretions but lower blood levels. Therefore, the aerosolized route places the drug where it is needed without the risk of side effects caused by prolonged elevation of serum levels.

In the same study, the patients receiving aerosolized antibiotics had a higher incidence of a clinical cure of pneumonia. Clearance of gram negative bacterial pathogens from the sputum was also greater in those patients treated by the tracheal route. Unfortunately, prolonged treatment with gentamicin in this manner was responsible for emergence of resistant strains of providentia, pseudomonas, and klebsiella (15).

Other groups have used aerosolized polymyxin for prophylaxis in seriously ill patients (16,17). Greenfield et al (8) has demonstrated a decreased

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13. Esrig BC, Stephenson SF, Fulton RL: Role of pulmonary infection in the pathogenesis of smoke inhalation. *Surg Forum* 26: 204-206, 1975.
  14. Berendt RF, Long GC, Walker JS: Treatment of respiratory klebsiella pneumoniae infection in mice with aerosols of kanamycin. *Antimicrob. Agents Chemoth* 8: 585-590, 1975.
  15. Klatersky J, Bogaerts AM, Noterman J, et al: Infections caused by providence bacilli. *Scand J Inf Dis* 6: 153-158, 1974.
  16. Feely TW, Moulin GC, Hedley-White J, et al: Aerosol polymyxin and pneumonia in seriously ill patients. *NEJM* 293: 471-475, 1975.
  17. Klick JM, Moulin GC, Hedley-White J, et al: Prevention of gram negative bacillary pneumonia using polymyxin aerosols as prophylaxis. *J Clin Invest* 55: 514-519, 1975.



colonization of the upper respiratory tract in patients so treated. But prolonged treatment also resulted in emergence of resistant strains which caused highly lethal pneumonitis. Overall mortality rates were not reduced in the patients receiving the aerosolized polymyxin as compared to controls.

Of further interest are the ventilatory effects of drugs given by the tracheal route. Dickie and de Groot (18) have examined kanamycin and polymyxin in this regard. Although kanamycin caused only minor changes, polymyxin was associated with a significant deterioration in vital capacity, flow rates, and maximum voluntary ventilation. Work done at this institute has not shown any effect of aerosolized gentamicin on pulmonary function.

This trial has failed to demonstrate any beneficial effect of aerosolized gentamicin on either mortality or morbidity of inhalation injury. Two factors are worthy of note. First, aerosolized antibiotics may have a beneficial effect on pulmonary pathophysiology caused by a limited exposure to bacteria. However, in the case of an extensive burn with its large amount of ongoing bacterial growth, continued seeding is a problem which antibiotics may not be able to overcome. Secondly, continued use of gentamicin resulted in resistant strains of klebsiella and pseudomonas emerging in both the burn wound and sputum. Thus, as other authors have shown, the use of prophylactic antibiotics may ultimately yield more problems than benefits.

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18. Dickie KJ, de Groot WJ: Ventilatory effects of aerosolized kanamycin and polymyxin. *Chest* 63: 694-697, 1973.

#### PRESENTATIONS AND/OR PUBLICATIONS:

None

RESEARCH AND TECHNOLOGY WORK UNIT SUMMARY				1. AGENCY ACCESSION*	2. DATE OF SUMMARY*	REPORT CONTROL SYMBOL DD-DR&E(AR)636	
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76 10 01	D. CHANGE	U	U	NA	NL	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	
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B. CONTRIBUTING							
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11. TITLE (Precede with Security Classification Code)* (U) Evaluation of Synthetic Sheeting as Operating Room Drape Material for Use in a Military Burn Unit (44)							
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F. CUM. AMT.							
19. RESPONSIBLE DOD ORGANIZATION				20. PERFORMING ORGANIZATION			
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				NAME: Robert B Lindberg, PhD			
				NAME:			
22. KEYWORDS (Precede EACH with Security Classification Code) (U) Military burn unit; (U) Operating room based infections; (U) Surgical drapes; (U) Surgical gowns							
23. TECHNICAL OBJECTIVE,* 24. APPROACH, 25. PROGRESS (Furnish individual paragraphs identified by number. Precede text of each with Security Classification Code.)							
<p>23. (U) Evaluation in terms of draping characteristics, absorbency, physician acceptance, and bacterial barrier qualities of a Spunbonded Olefin-cellulosic Laminated sheeting as surgical drapes and gowns. A decrease in bacterial seeding of operative wounds via drapes will minimize postoperative wound infections decreasing subsequent morbidity and mortality in injured troops.</p> <p>24. (U) Laboratory assessment of bacterial barrier properties of synthetic sheeting. Clinical use of drapes on burn patients to determine surgeon acceptability. Photographic documentation of draping characteristics, absorbency, and "run-off." Pre- and postoperative cultures at margin of operative field. Temperature monitoring to determine heat transmission characteristics.</p> <p>25. (U) 76 10 - 77 09 Bacterial barrier properties of additional drape material samples have been assessed in the laboratory and the results analyzed. Eleven samples have been tested with penetration of five different bacteria determined for each sample in replicate trials. Penetration rate ranged from 3% to 19.5% of all sites. One sample of apparent greater density appeared to have effective barrier properties and three samples appeared to be moderately effective. Further testing of materials patterned after the sample with effective barrier properties is planned.</p>							

\* Available to contractors upon originator's approval.

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ANNUAL PROGRESS REPORT

PROJECT NO. 3S1611102BS05, MILITARY BURN RESEARCH

REPORT TITLE: EVALUATION OF SYNTHETIC SHEETING AS OPERATING ROOM DRAPE  
MATERIAL FOR USE IN A MILITARY BURN UNIT

US ARMY INSTITUTE OF SURGICAL RESEARCH  
BROOKE ARMY MEDICAL CENTER  
FORT SAM HOUSTON, TEXAS 78234

1 October 1976 - 30 September 1977

Investigators:

Basil A. Pruitt, Jr., MD, FACS, Colonel, MC  
Robert B. Lindberg, PhD  
Arthur D. Mason, Jr., MD

Reports Control Symbol MEDDH-288(R1)

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## ABSTRACT

PROJECT NO. 3S1611102BS05, MILITARY BURN RESEARCH

REPORT TITLE: EVALUATION OF SYNTHETIC SHEETING AS OPERATING ROOM  
DRAPE MATERIAL FOR USE IN A MILITARY BURN UNIT

US Army Institute of Surgical Research, Brooke Army Medical Center, Fort  
Sam Houston, Texas 78234

Period covered in this report: 1 October 1976 - 30 September 1977

Investigators: Basil A. Pruitt, Jr., MD, FACS, Colonel, MC  
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Reports Control Symbol MEDDH-288(R1)

The bacterial barrier properties of eleven coded samples of synthetic surgical drape material have been assessed using bacterial penetrability tests developed at this Institute. The penetration of five bacterial organisms each suspended in liquid culture media and inoculated at six sites on circular samples of each drape material was determined in seven replicate trials of each material.

Penetration rates differed significantly between drape materials and ranged from 3% to 99.5%. One consistently "best" drape material was identified which permitted penetration of only 3% of all inoculation sites. Three other materials appeared to be moderately effective bacterial barriers with penetration of from 12-16% of inoculation sites. All other materials showed greater penetration rates and appeared to be ineffective microbial barriers. The highly effective barrier appeared to be of more dense construction. Further testing is planned on samples of materials patterned after the effective barrier material.

Military burn unit  
Operating room based infections  
Surgical drapes  
Surgical gowns



## EVALUATION OF SYNTHETIC SHEETING AS OPERATING ROOM DRAPE MATERIAL FOR USE IN A MILITARY BURN UNIT

Conventional surgical drapes made of cotton, even when tightly woven, are imperfect bacterial barriers and as such, inadequately protect operative wounds of combat injured soldiers from contamination. Surgical drapes fabricated from synthetic fibers have either been poorly accepted by surgeons because of poor draping characteristics, liquid run-off and poor heat transmission, or if softened to avoid those limitations, have possessed compromised barrier properties and permitted passage of test bacteria. Spun-bonded Olefin sheeting of varying thickness and "tightness" of weave is being evaluated to define those characteristics of a clinically acceptable surgical drape material which will provide reliable bacterial barrier.

### Methods

Discs 85 mm in diameter were cut from each of eleven synthetic sheeting material samples and sterilized with ethylene oxide in glass Petri dishes. Assay strains of Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella pneumoniae, Escherichia coli and Serratia marcescens were activated from frozen stock and each strain was passed serially through broth three times prior to use in testing. Discs of each drape material were placed individually on the surface of blood agar plates and drops of 0.07 ml of the broth culture were placed equidistant in a circle 1 cm from the edge of the material. Six drops were used on each plate and seven replications of this test were made for each organism.

Following four hours exposure of the material to the broth culture at room temperature any remaining fluid was removed with a Pasteur pipette and the disc of drape material removed from the agar plate. The agar plates were incubated at 37°C for 24 hours and then assessed in terms of growth of bacteria that had passed through individual inoculation sites. If confluent growth occurred extending to two inoculation sites each of the sites involved was rated as positive although it was theoretically possible for a single breakthrough to spread over adjacent sites under the paper disc.

### Results

The percentage of penetration of inoculum sites of each sheeting sample is shown in the table. As can be seen sample 77-1-2 appears to be the most effective barrier with penetration of only 3% of all inoculation sites. Samples 77-1-1, 77-1-4, and 77-1-5 appear to be moderately effective barriers although they permitted penetration at 16, 12, and 16% of inoculation sites respectively.

TABLE I  
Bacterial Penetration of Drape Material Samples

<u>Sample Code</u>	<u>Bacterial Penetration</u>			<u>% Penetration</u>
	<u>Sites of</u> Penetration/Inoculation	<u>Total</u> Sites		
77-1-1	32	/	204	16
77-1-2	6	/	210	3
77-1-3	50	/	210	24
77-1-4	24	/	204	12
77-1-5	34	/	210	16
77-1-6	106	/	210	50
77-1-7	170	/	210	81
77-1-8	52	/	204	25
77-1-9	200	/	210	95
77-1-10	52	/	210	25
77-1-11	209	/	210	99.5

#### Discussion

Although the majority of samples tested possessed ineffective barrier properties with penetration of bacteria at from 24-99.5% of inoculation sites one material appeared to be a highly effective barrier and three others appeared to be moderately effective bacterial barriers. The sample showing highly effective barrier properties permitted the passage of Pseudomonas aeruginosa at one of 42 inoculation sites, of Klebsiella pneumoniae, at two of 42 inoculation sites, of Klebsiella pneumoniae, at two of 42 inoculation sites, and penetration of Serratia marcescens, at three of 42 inoculation sites. The limited penetration of this drape material by Pseudomonas aeruginosa is particularly encouraging since that organism has been found by previous testing to be the organism in the test battery most adept at traversing drape material.

Counting of positive penetration has, as noted above, been conservative with two inoculum sites considered to show penetration of a single area of bacterial colonization touched two inoculation sites. Such a procedure is felt justified since it indicates at least a compromise of the sample's barrier properties.

The "highly effective" barrier material appears to be of more dense construction than the other materials and such may indicate a fabrication requirement to produce a material with reliable barrier properties. Further testing is planned during the forthcoming year to assess the barrier properties of other materials patterned after this "highly effective" sheeting.

RESEARCH AND TECHNOLOGY WORK UNIT SUMMARY						1. AGENCY ACCESSION <sup>a</sup>	2. DATE OF SUMMARY <sup>a</sup>	REPORT CONTROL SYMBOL DD-DR&E(AR)636	
3. DATE PREV. SUMM <sup>a</sup>	4. KIND OF SUMMARY	5. SUMMARY SCTY <sup>a</sup>	6. WORK SECURITY <sup>a</sup>	7. REGRADING <sup>a</sup>	8. DISB <sup>a</sup> INSTR <sup>a</sup>	9. SPECIFIC DATA - CONTRACTOR ACCESS <sup>a</sup>		10. LEVEL OF SUM <sup>a</sup>	
76 10 01	D. CHANGE	U	U	NA	NL	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO		A. WORK UNIT	
10. NO./CODES <sup>a</sup>		PROGRAM ELEMENT		PROJECT NUMBER		TASK AREA NUMBER		WORK UNIT NUMBER	
a. PRIMARY		62774A		3S762774A820		00		115	
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11. TITLE (Precede with Security Classification Code) <sup>a</sup>									
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						NAME:			
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(U) Burn injury; (U) Topical therapy; (U) Sulfamylon; (U) Wound excision; (U) 5% Sulfamylon acetate solution; (U) Humans; (U) Autografts									
23. TECHNICAL OBJECTIVE <sup>a</sup> 24. APPROACH, 25. PROGRESS (Furnish individual paragraphs identified by number. Precede text of each with Security Classification Code.)									
23. (U) The military relevance of improving burn wound care will be realized in increased troop survival following thermal injury. Newer methods under current investigation include the use of 5% aqueous sulfamylon soaks, excision of eschar from burned soldiers, planned evaluation of cerium silver sulfadiazine and the use of frozen homograft in burn wound care. Our objective is to further define the use of these methods.									
24. (U) Patients admitted to the Institute of Surgical Research for care of thermal injuries receive burn wound care based on the specific injury. Under appropriate conditions, 5% aqueous Sulfamylon soaks, excision of the eschar, and other modalities of wound care may be used. Establishment of a frozen homograft bank to evaluate the use of this product is being undertaken.									
25. (U) 76 10 - 77 09 A total of 116 patients during this year had sulfa soaks employed for the purpose of dressings to the burn wound and 100 patients had sulfa soaks used in conjunction with skin grafting. A 0.9% incidence of significant skin reactions was noted as the only significant adverse reactions to the medication and these results support its continued use on a routine basis. Burn wound excision continued to be extensively utilized in an attempt to decrease the burn wound size and reduce the infectious complications. Tangential, full thickness excision to viable fat, and formal excision to fascia are all utilized and undergoing continued evaluation. Interest in the use of frozen homograft to maintain a continuous adequate supply of highest quality biologic dressing has resulted in an attempt to establish a frozen homograft bank to further evaluate the use of this product. On the basis of "pilot" studies elsewhere suggesting cerium silver sulfadiazine to be an effective topical agent, a clinical trial in collaboration with other burn units is being planned to evaluate the efficacy of that agent in controlling burn wound flora.									

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ANNUAL PROGRESS REPORT

PROJECT NO. 3S762774A820-00 MILITARY BURN TECHNOLOGY

REPORT TITLE: EVALUATION OF BURN WOUND CARE IN TROOPS WITH BURN INJURY:  
5% AQUEOUS SULFAMYLON SOAKS USED IN TOPICAL TREATMENT OF  
BURNED SOLDIERS

US ARMY INSTITUTE OF SURGICAL RESEARCH  
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ABSTRACT

PROJECT NO. 3S762774A820-00 MILITARY BURN TECHNOLOGY

REPORT TITLE: EVALUATION OF BURN WOUND CARE IN TROOPS WITH BURN INJURY:  
5% AQUEOUS SULFAMYLON SOAKS USED IN TOPICAL TREATMENT OF  
BURNED SOLDIERS

US Army Institute of Surgical Research, Brooke Army Medical Center, Fort  
Sam Houston, Texas 78234

Period covered in this report: 1 October 1976 - 30 September 1977

Investigators: Richard C. Treat, M.D., Major, MC  
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Reports Control Symbol MEDDH-288(R1)

Improvement in care of the burn wound continues to be a major goal of the Institute of Surgical Research. Newer methods under current investigation includes the use of 5% aqueous Sulfamylon soaked dressings. Patients admitted to the Institute of Surgical Research for treatment of thermal injuries receive burn wound care based on specific injury needs. Under appropriate conditions 5% aqueous Sulfamylon soaked dressings are utilized. A total of 116 patients during this year had Sulfamylon soaks employed for the purpose of dressings to the burn wound and 100 patients had Sulfamylon soaked dressings used following skin grafting. A 0.9% incidence of significant skin rash was noted as the only significant adverse reaction due to this medication. These results support its continued use on a routine basis.

Burn injury  
Topical therapy  
5% Sulfamylon acetate solution  
Humans

EVALUATION OF BURN WOUND CARE IN TROOPS WITH BURN INJURY: 5% AQUEOUS  
SULFAMYLON SOAKS USED IN TOPICAL TREATMENT OF BURNED SOLDIERS

The evaluation of 5% Sulfamylon acetate solution as used in the topical treatment of burn wounds has been continued at this Institute. During the reporting period 1976 260 patients were admitted to the U.S. Army Institute of Surgical Research. Of these 260 patients, 116 had dressings employed for burn wound care which were wetted with the Sulfamylon solution. During this same period, 100 patients had the application of Sulfamylon soaked dressings in conjunction with skin grafting procedures. Most of these patients had the Sulfamylon solution soaked dressings used for both wound preparation and following grafting procedures. The Sulfamylon acetate soaked dressings are used either as continuous wet dressings in preparing a wound for skin grafting or as wet to dry dressings utilized for debridement of burn wounds. Following most grafting procedures wherever "meshed" grafts are applied dressings soaked with the 5% Sulfamylon acetate solution are applied in an attempt to decrease bacterial growth and protect the graft.

Occasional respiratory problems mainly in the form of hyperventilation have been noted in some patients who have had the application of Sulfamylon soaked dressings to extensive ungrafted burn wound. This hyperventilation uniformly resolves following discontinuance of the application of the Sulfamylon solution to the dressings. Skin allergies to the sulfa solution continue to be noted with seven such reactions recorded in the 116 patients receiving the Sulfamylon soaked dressings. This represents an incidence of 6% allergic skin reactions. Six patients who developed allergic reactions had rapid resolution following administration of an antihistamine and the 5% Sulfamylon solution soaked dressings could be continued. In one instance a severe widespread urticarial reaction required that use of the medication be stopped. This represents a 0.9% incidence of significant skin reactions to the 5% Sulfamylon acetate soaked dressings. No other adverse reactions were noted in reviewing the clinical course and laboratory data of this group of patients.

The use of 5% Sulfamylon acetate soaked dressings continues to be an important component of the treatment of burn patients both in the preparation of burn wounds for grafting and in the protection of "meshed" grafts once placed. Its widespread use in severely burned patients with a low incidence of allergic reactions and absence of other side effects support its continued use in burn treatment.

ANNUAL PROGRESS REPORT

PROJECT NO. 3S762774A820-00 MILITARY BURN TECHNOLOGY

REPORT TITLE: EVALUATION OF BURN WOUND CARE IN TROOPS WITH BURN INJURY:  
EXCISION OF ESCHAR IN BURNED SOLDIERS

US ARMY INSTITUTE OF SURGICAL RESEARCH  
BROOKE ARMY MEDICAL CENTER  
FORT SAM HOUSTON, TEXAS 78234

1 October 1976 - 30 September 1977

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ABSTRACT

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Improvement in care of the burn wound continues to be a major goal of the Institute of Surgical Research. Newer methods under current investigation include excision of eschar from burned soldiers. Patients admitted to the Institute of Surgical Research for treatment of thermal injuries receive burn wound care based on specific injury needs. Under appropriate conditions excision of eschar is utilized. Burn wound excision continued to be utilized in an attempt to decrease the burn wound size and reduce septic complications. Tangential, full thickness excision to viable fat, and excision to the level of investing fascia continue to be evaluated.

Burn injury  
Wound excision  
Humans



EVALUATION OF BURN WOUND CARE IN TROOPS WITH BURN INJURY:  
EXCISION OF ESCHAR IN BURNED SOLDIERS

Excision of the burn wound at the U.S. Army Institute of Surgical Research has taken three forms. The first being excision of the burn wound and subcutaneous tissue to the investing fascia, the second tangential excision with immediate grafting, and thirdly escharectomy with preparation of the underlying bed for later autografting. Excision to the investing fascia is done in two categories of patients at the Institute of Surgical Research. In massive burns, those greater than 70% of the total body surface where fatal outcome is nearly always expected due to sepsis from the burn wound, excision to fascia and coverage with either allograft or xenograft is performed. Patients in this category during 1976 had a uniformly fatal outcome. One patient with a 92% total body surface full thickness injury was excised in three sittings and initially maintained in allograft. At the time of his death from a pulmonary complication he was approximately 65% covered with autograft. If the pulmonary complication could have been avoided he would have represented a possible survivor. Another category of patients are those having 40-60% total body surface burn with localized areas of third degree burn, especially patients with lower extremity injuries which frequently are associated with septic complications. Patients in this category have been excised to fascia and either autografted or allografted at the same sitting with improved outcome. New vistas for excision to the investing fascia in the coming years may be the use of immunosuppression allowing the allograft to remain in place for a longer time, the development of a synthetic material which can be used in place of allograft and will remain adherent to the wound preventing establishment of infection, or an unlimited source of allograft most likely through the use of frozen allograft.

Tangential excision as described by Douglas Jackson has been used at our unit for approximately three years for the treatment of deep second degree burns of the hand. It is our opinion that hand burns may be divided into three categories when first seen. The first category being those burns which are wet, sensitive to pin prick and blanch upon pressure. These can be treated in any standard fashion and may be expected to heal in less than three weeks with a serviceable epithelial covering. The second category are the deep second degree burns which are insensitive, white, do not blanch to pressure and are dry on the surface. These will heal in five to eight weeks but usually with a very unacceptable epithelial covering which tends toward hypertrophic scarring. These hands are best treated by tangential excision and immediate grafting. The third category are those hands that have obvious deep involvement at the time of admission characterized by waxy appearance of the eschar, desiccated digits and thrombosed vessels on the dorsum. All attempts at surgical excision of this type of hand have ended with a functionally worse result than if treated in a conservative fashion. Therefore tangential excision is limited to the category two burns, those being deep

second, which will eventually heal but with a very poor epithelial covering. The surgical procedure involves tangential excision of the nonviable tissue until a freely bleeding dermal bed is encountered. At this time a hemostatic agent is placed on the bed and once the wound is dry, the hand is placed on a hand splint and covered with 1 1/2:1 meshed autograft. We have had uniformly excellent results with tangential excision and immediate placement of autograft. The goals of improved functional capabilities with satisfactory epithelial covering are usually achieved in properly selected patients.

Escharectomy has been utilized both in the early and later post burn course at the Institute of Surgical Research. Two forms of this type of excision are practiced. Excision of the entire eschar with a guarded knife down to freely bleeding fat followed by application of allograft, xenograft or sulfa soaks to the excised area is most commonly performed. Dressings are changed every two days and within seven to 14 days a lush bed of granulation tissue develops. This can be autografted and will greatly speed the patients hospital course. The second form of escharectomy utilizes a guarded skin graft knife to remove the eschar until the first sign of bleeding is noted. At this point the patient may be placed in xenograft or wet dressings and the process repeated every 48 hours until all necrotic tissue is removed. This has the advantages of being able to be performed on adults without a general anesthetic and significant blood loss. However, it requires longer to prepare the bed for definitive grafting. Escharectomy may also be performed in tenacious eschars during the third or fourth week post burn. The entire eschar is removed, however the blood loss can be massive so no more than 15-20% of the total body surface should be done at one time and the extremities should be done under tourniquet whenever possible.

All thermally injured patients admitted to the United States Army Institute of Surgical Research from 1973 through 1976 were reviewed in order to determine the efficacy of excision of the burn wound to fascia as a therapeutic modality. Out of 1013 admissions, 72 patients (7%) underwent this procedure. The excised patients had a mean total burn size of 52% of the body surface and a mean third degree burn of 33%. They had an overall mortality of 57% and a morbidity of 60%.

When compared to the entire burn population, excision to fascia in patients with greater than a 60% surface burn had no effect on mortality (86 vs 93%). In patients with moderate size burns (40-60%), excision to fascia decreased mortality compared to the parent population (38 vs 50%). In patients with burns involving less than 40% of surface area, excision to fascia increased mortality from 10 to 20%. However, this procedure had been employed in patients with evidence of burn wound invasion which is associated with an almost 100% mortality. Therefore, this procedure salvaged 62% of the patients with moderate size burns and 80% of patients with burns of less than 40% of the body surface.

Excision within the first 72 hours postburn was not associated with an improved mortality rate compared to excision later.

ANNUAL PROGRESS REPORT

PROJECT NO. 3S762774A82Q-QQ MILITARY BURN TECHNOLOGY

REPORT TITLE: EVALUATION OF BURN WOUND CARE IN TROOPS WITH BURN INJURY:  
FROZEN HOMOGRAFT

US ARMY INSTITUTE OF SURGICAL RESEARCH  
BROOKE ARMY MEDICAL CENTER  
FORT SAM HOUSTON, TEXAS 78234

1 October 1976 - 30 September 1977

Investigators:

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Reports Control Symbol MEDDH-288(R1)

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ABSTRACT

PROJECT NO. 3S762774A820-00 MILITARY BURN TECHNOLOGY

REPORT TITLE: EVALUATION OF BURN WOUND CARE IN TROOPS WITH BURN INJURY:  
FROZEN HOMOGRAFT

US Army Institute of Surgical Research, Brooke Army Medical Center, Fort  
Sam Houston, Texas 78234

Period covered in this report: 1 October 1976 - 30 September 1977

Investigators: Richard C. Treat, M.D., Major, MC  
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Improvement in care of the burn wound continues to be a major goal of the Institute of Surgical Research. Newer methods under current investigation includes the use of frozen homograft in burn wound care. Patients admitted to the Institute of Surgical Research for treatment of thermal injuries receive burn wound care based on specific injury needs. An evaluation to determine the feasibility for establishment of a frozen homograft bank is also being undertaken. Interest in the use of frozen homograft as a source of biologic dressing has resulted in an attempt to establish a frozen homograft bank and to further evaluate the use of this product.

Burn injury  
Humans  
Autografts

EVALUATION OF BURN WOUND CARE IN TROOPS WITH BURN INJURY:  
FROZEN HOMOGRAFT

Human allograft skin is presently used extensively at our Burn Unit. It has mainly been utilized as an immediate, temporary wound coverage following excisions of burn wounds to the level of the investing fascia. A recent review by Drs. Levine and Sirinek of our unit has shown that in patients with moderate size burns (40-60% TBS), excision to fascia decreased mortality compared to the parent population (38 vs 50%). Although commercially available porcine xenograft skin can also be used in these procedures, it is not as effective as cutaneous allograft. The unique characteristic of allograft skin is its ability to become vascularized until rejection takes place. Allograft skin is also used to cover granulation tissue between "crops" of autograft in patients with extensive burns, to prepare debrided wounds for autografting, and to protect exposed, uninjured tissues. In addition, we are currently evaluating the use of biologic dressings to cover and protect expanded, meshed autograft, especially that applied immediately following burn wound excisions.

At present, our only source of allograft skin is fresh or "icebox" fresh skin, limiting us to two weeks' storage of procured skin. Thus, at times when allograft skin is unavailable, we cannot perform excision procedures on some patients. In addition, we are unable to stockpile large amounts of allograft skin for use in case of a mass casualty situation e.g., the Tenerife disaster. Reports from the burn centers in Boston and Dallas have attested to favorable clinical experience with the use of long-term frozen human skin, stored in a skin bank. Currently, we are planning the development of such a bank. This is to include evaluation of new techniques in freezing and storing such skin and also improved protocols for harvesting allograft skin in Armed Forces Medical Centers.

We are currently evaluating the following equipment to be used in such a frozen skin bank: 1) a laminar air flow hood under which to process the allograft skin; 2) a controlled-rate freezer for initial lowering of the temperature of the specimens to  $-70^{\circ}\text{C}$ ; 3) a liquid nitrogen freezer for long-term storage of the allograft skin at  $-180$  to  $-190^{\circ}\text{C}$ .

RESEARCH AND TECHNOLOGY WORK UNIT SUMMARY				1. AGENCY ACCESSION <sup>a</sup>	2. DATE OF SUMMARY <sup>a</sup>	REPORT CONTROL SYMBOL DD-DR&E(AR)636	
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76 10 01	D. CHANGE	U	U	NA	NL	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	A. WORK UNIT
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NAME: US Army Institute of Surgical Research				NAME: US Army Institute of Surgical Research			
ADDRESS: Ft Sam Houston, Tx 78234				Microbiology Branch			
				ADDRESS: Ft Sam Houston, Tx 78234			
RESPONSIBLE INDIVIDUAL				PRINCIPAL INVESTIGATOR (Furnish SSAN if U.S. Academic Institution)			
NAME: Basil A Pruitt, Jr, COL, MC				NAME: Robert B Lindberg, PhD			
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23. TECHNICAL OBJECTIVE, 24. APPROACH, 25. PROGRESS (Furnish individual paragraphs identified by number. Precede text of each with Security Classification Code.) 23. (U) Burns are a major part of military injuries in combat and the military relevance of this research lies in the fact that infection and resultant sepsis are the major problems in burned soldiers. Control of surface infection is pursued empirically and simultaneously mechanisms of infection, epidemiology and topical chemotherapy are assessed in relation to causative bacterial species.  24. (U) Culture of burn wounds and other infection sites, strain differentiation of major opportunistic pathogens and endotoxin assay are carried out. Assessment of virulence and testing of new antimicrobial drugs are performed on experimental models of burn wound sepsis.  25. (U) 76 10 - 77 09 Epidemics of <u>Kleb. pneumoniae</u> , <u>Enterobacter cloacae</u> , <u>Staph. aureus</u> and <u>Pseudomonas aeruginosa</u> occurred in burn wounds despite intensive topical therapy with Silvadene (R) and Sulfamylon; oxidative species were not conspicuous. Sulfamylon resistance did not appear; with new technics developed here, silver sensitivity was shown to vary unexpectedly with nosocomial infections. Monotype epidemics of <u>Staph. aureus</u> and <u>Pseudomonas aeruginosa</u> occurred; fluctuations in antibiotic sensitivity were greatest with Staphylococci, in which Nafcillin resistance was higher than that of methicillin. Cross resistance exacerbated this problem. Fungi were rare in burns. Sulfanamide (compounds with Zn, Cu, Ce, and Cr) were assessed; several with therapeutic potential were recognized. Phage typing of <u>Serratia</u> approached completion of an effective system. A stable-blind trial of J-5 antiserum in therapy of sepsis is in progress.							

<sup>a</sup> Available to contractors upon originator's approval.

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PREVIOUS EDITIONS OF THIS FORM ARE OBSOLETE. DD FORMS 1498A, 1 NOV 65 AND 1498-1, 1 MAR 66 (FOR ARMY USE) ARE OBSOLETE

ANNUAL PROGRESS REPORT

PROJECT NO. 3S762774A820-00, MILITARY BURN TECHNOLOGY

REPORT TITLE: STUDIES OF INFECTION AND MICROBIOLOGIC SURVEILLANCE  
OF TROOPS WITH THERMAL INJURY -- ANTIBIOTIC  
SENSITIVITY OF CURRENT MILITARY BURN PATIENT FLORA

US ARMY INSTITUTE OF SURGICAL RESEARCH  
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1 October 1976 - 30 September 1977

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## ABSTRACT

PROJECT NO. 3S762774A820-00, MILITARY BURN TECHNOLOGY

REPORT TITLE: STUDIES OF INFECTION AND MICROBIOLOGIC SURVEILLANCE  
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Eight hundred forty-five strains of bacteria were recovered in blood cultures taken from burn patients with bacteremia and septicemia. Methicillin-resistance in Staphylococcus aureus remained a significant problem, with virtual disappearance of susceptibility to nafcilli. Vancomycin, Keflin, minocin, clindamycin and vibramycin were maximally active in vitro. Klebsiella pneumoniae and Pseudomonas aeruginosa were the most common gram-negative invading species. Strains of the former were responsive primarily to minocin, vibramycin, colymycin and amikacin. Therapeutic response to Klebsiella sepsis was seldom encouraging. For Pseudomonas, gentamicin resistance was virtually complete in 1977. Optimal in vitro results were achieved with amikacin and colymycin. Carbenicillin was effective in 60% of strains, as were minocin and tobramycin. Again, therapeutic response in Pseudomonas sepsis was unimpressive.

Antibiotic sensitivity  
Pseudomonas  
Burn wounds  
Chemotherapy  
Klebsiella

STUDIES OF INFECTION AND MICROBIOLOGIC SURVEILLANCE  
OF TROOPS WITH THERMAL INJURY --  
ANTIBIOTIC SENSITIVITY OF CURRENT MILITARY BURN  
PATIENT FLORA

Bacterial sepsis remains the major cause of death in burn injury. Since the only significant means of coping with this grave involvement is antimicrobial prophylaxis therapy, knowledge of sensitivity of the prominent offending bacterial species is essential.

In this Institute major emphasis is placed on testing of strains recovered from blood culture, since these strains present an obvious threat to the patients' survival. In previous reports, a small number of strains from other sources were studied. In this reporting period, however, virtually all strains tested were from blood cultures.

The spectrum of sensitivity of current clinical isolates is the most useful guide to selection of an optimal antibiotic regimen in a patient whose condition makes prompt institution of therapy desirable. Changes from sensitive to resistant and *vice versa* are frequent in the bacterial flora of burn patients, and continued monitoring of this flora offers insight into these changes and a basis for improved understanding of changes in antibiotic sensitivity of microorganisms. Analysis of trends in antibiograms also offers a clue to the presence of new strains, which periodically enter the burn population, at times with a resultant increase in sepsis and infections associated with a new strain of an opportunistic pathogen.

#### TECHNIC AND STRAINS

The Minimum Inhibitory Concentration (MIC) technic has been used routinely in this laboratory for many years. The technic was described in a previous report (1). Pre-loaded tubes containing 1.0 ml amounts of antibiotic in concentrations from 50 ug/ml to 1.56 ug/ml in Trypticase Soy Broth (TSB) are seeded with 1.0 ml of a 4 to 6 hour TSB culture containing  $10^4$  to  $10^5$  organisms per ml. After 18 to 20 hours of incubation inhibitory endpoints are read by inspection. MIC is the lowest concentration of antibiotic to prevent growth. Minimum Bactericidal Concentration, when desired, could be determined by subculturing tubes at concentrations above the visible growth level.

Ten species of bacteria were tested in meaningful numbers. These are listed in Table 1. The major species responsible for sepsis were, in order of numbers recovered, Staphylococcus aureus, Pseudomonas aeruginosa, and

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1. Lindberg RB, Contreras AA, Smith HOD, Jr, Plowey EC, Mason AD, Jr: Antibiotic Sensitivity of current military burn patient flora. USA Inst Surg Res Annual Rpt FY 1973. Brooke Army Medical Center, Fort Sam Houston, Texas. Section 7.

Table 1. Species of Bacteria and Number of Patients with Strains Tested for Antibiotic MIC

Species	1976		1977		Total Strains
	Patients	Strains	Patients	Strains	
Staph. aureus	43	125	50	75	200
Staph. epidermidis	21	36	28	66	102
Strep spp (alpha, non-hemol)	9	13	15	31	44
Ps. aeruginosa	42	94	42	90	184
Kleb. pneumoniae	60	145	19	32	177
Enterob. cloacae	2	2	28	41	43
E. coli	10	11	15	23	34
S. marcescens	2	4	7	10	14
Proteus mirabilis	6	11	10	19	30
Citrobacter freundii	1	2	8	15	17
		443		402	845

Sources: With 6 exceptions, all strains were from blood cultures.

Klebsiella pneumoniae. Enterobacter cloacae, formerly a major opportunistic invader, was virtually not seen in 1976; in 1977, its incidence rose markedly, and it was the second most common gram-negative species. Other species which have in the past year been recovered from blood with increasing frequency were Escherichia coli and Proteus mirabilis.

The selection of antibiotics for MIC testing is subject to frequent review and the test battery has been altered from time to time. The current set is shown in Table 2. Every major category of antibiotic is included. Lincocin was removed from this set in 1976 and replaced with clindamycin, of the lincocin group.

#### SENSITIVITY OF BURN PATIENT FLORA TO ANTIBIOTICS

The following tables summarize the sensitivity of the principal species of bacteria which cause or are associated with, sepsis in burns. Results are presented in cumulative increments. Since blood levels achievable are a defining characteristic of antibiotic sensitivity, each antibiotic could be rated separately as to the level of inhibition associated with the designation "sensitive". For convenience and comparability, the sensitive-resistant borderline has been set at 6.5 ug/ml for gram-positive microorganisms, and 12.5 ug/ml for gram-negative bacteria (2)

2. Finland M: Changing patterns of susceptibility of common bacterial pathogens to antimicrobial agents. Ann Int Med 26: 1009, 1972.

Table 2. Antibiotics Used in MIC Test for  
Sensitivity of Bacteria: 1976-1977

<u>Gram-Positive</u>		<u>Gram-Negative</u>	
Gentamicin	: G	Gentamicin	
Methicillin	: Sc	-	
Oxacillin	: Ps	-	
Nafcillin	: U	-	
Minocin	: M	Minocin	
Keflin	: Kf	Keflin	
Vancomycin	: Va	-	
Clindamycin	: Cl	-	
Vibramycin	: Vb	Vibramycin	
Tobramycin	: To	Tobramycin	
		Kanamycin	: K
		Amikacin	: Ak
		Colistin	: Co
		Carbenicillin	: Cb
		Penicillin G	: Pen G
For <u>Ps. aeruginosa</u> :			
For <u>Proteus mirabilis</u> :			

Staphylococcus aureus: The interval covered in this period was 21 months instead of the customary 12. Hence changes of susceptibility pattern would risk being obscured in an overall summary of the 21 months. In the case of staphylococci, the strains are reported in two increments, 1976 and nine months of 1977 (Table 3). Methicillin-resistance has been of particular interest, since earlier reports showed appearance of a very high degree of resistance developing, following by a reappearance of susceptible forms. A parallel change in response to gentamicin had been observed. In 1976 only 23% of strains were methicillin-sensitive, while oxacillin was effective against 76% of all strains, with nafcillin at an intermediate level of 49%. This relationship was altered in 1977 when nafcillin-sensitive strains virtually disappeared. The other two semi-synthetic penicillins remained relatively unchanged in degree of effectiveness during this period. There was a parallel but less complete shift in behavior of gentamicin in 1977. Minocin, Keflin, vancomycin and clindamycin were each effective against the entire population of staphylococci tested. A drop in effectiveness of tobramycin from 100% to 65% effective at 6.5 ug/ml occurred in 1976.

It is to be pointed out that the level of effectiveness of this spectrum of antibiotics during 1976-1977 was not paralleled by similar clinical effectiveness. The fact that in at least 15 patients prolonged staphylococcemia occurred suggests that in vitro susceptibility was not always paralleled by clinical response.

Retrospective comparison of previous years is illuminating in the case of staphylococcus infections. The response of septicemic strains to antibiotics



Table 3. *Staphylococcus aureus*: Cumulative Inhibitory Levels for  
200 Strains: 1976-1977 (Jan-Sept)

Antibiotic Level ug/ml	Antibiotic and Per Cent Inhibited									
	G	Sc	Ps	U	M	Kf	Va	Cl	Vb	To
<u>1976</u>										
25	96	90	97	81	99	97	100	97	100	100
12.5	89	79	93	57	98	96	100	96	99	100
6.2	50	23	70	49	93	94	100	95	94	100
3.1	8	1	28	44	61	94	98	95	28	88
<u>1977</u>										
25	76	98	79	41	100	99	100	99	100	69
12.5	71	93	77	52	100	98	100	98	100	69
6.2	31	36	65	2	94	97	100	97	97	65
3.1	17	6	38	1	62	96	95	90	20	50
Total Tested:	1976 - 125		1977 - 75							

G: Gentamicin; Sc: Methicillin; Ps: Oxacillin; M: Minocin; Kf: Keflin; Va: Vancomycin;  
Cl: Clindamycin; Vb: Vibramycin; To: Tobramycin

since 1970 is presented in Table 4. The proportion of strains inhibited by 6.25 ug/ml in each increment is shown. The methicillin group has been of particular interest. Methicillin itself has, from 1970 through 1976, been the least effective antibiotic, with inhibitory action ranging from a low of 13.1% of strains in 1972 to a high of 65.2% of strains in 1974. Oxacillin was more effective than methicillin during the low ebb of 1970-1972, and remained active against at least 65% of strains during 1976 and 1977 drop in methicillin effectiveness. The response to these three methicillin-type antibiotics did not appear to be linked, since a total drop in effectiveness of nafcillin occurred when methicillin effectiveness was increasing. Cephalothin activity paralleled that of methicillin in 1972, but in subsequent years has remained high; Keflin was one of the most effective antibiotics in 1975-1977. The drop in effectiveness of gentamicin and minocin in 1975 was transitory both of these antibiotics have since been at the level of maximum effectiveness.

Table 4. Comparative Sensitivity of Staphylococcus aureus on an Annual Basis: 1970-1977 (Jan-Sept)

Antibiotic	Year and Per Cent of Strains Inhibited at 6.25 ug/ml							
	1970	1971	1972	1973	1974	1975	1976	1977
Gentamicin	32.0	50.0	35.0	67.9	92.2	38.8	50.0	30.6
Methicillin	18.0	15.5	13.1	50.0	65.2	21.8	23.5	35.7
Oxacillin	22.4	20.1	18.8	69.7	82.6	73.6	70.5	65.1
Nafcillin	33.9	33.0	26.0	62.3	83.3	85.6	49.5	1.8
Minocin	-	-	-	84.1	96.0	46.5	92.8	93.9
Keflin	-	56.4	22.6	72.1	90.4	97.2	94.0	97.1
Vancomycin	-	-	-	-	-	100.0	100.0	100.0
Clindamycin	-	-	-	40.7	95.8	98.0	95.6	97.1
Vibramycin	-	-	-	-	-	78.3	94.2	96.9
Tobramycin	-	-	-	-	-	88.8	100.0	65.4

Staphylococcus epidermidis: A rise from six strains recovered in 1975 to 102 strains recovered in 1976-1977 prompted inclusion of this species in this resume of antibiotic sensitivity (Table 5). These strains are commonly regarded as contaminants in blood culture; however in four patients out of 28, repeated isolation of the same strain were recorded. In any event, the presence of a strain in blood culture requires that it be tested; coagulase-negative staphylococci can be pathogenic, especially in stressed or immunologically deficient hosts. The proportion of strains sensitive to aminoglycosides and to methicillin type antibiotics was higher than that found with Staph. aureus. However, the relative sensitivity to methicillin, oxacillin and nafcillin was parallel to that observed with Staph. aureus. The remaining antibiotics were relatively effective against Staph. epidermidis, but the reactions were more heterogeneous. From 10% to 20% of strains were resistant to the antibiotics used in this assessment. The increase in recovery of Staph. epidermidis may represent more frequent invasion of burned patients or may be a result of more assiduous testing, since the rate of

Table 5. Staphylococcus epidermidis: Cumulative Inhibitory Levels  
for 102 Strains: 1976-1977 (Jan-Sep)

Antibiotic Level ug/ml	G	Sc	Antibiotic and Per Cent Inhibited						Va	Cl	Vb	To
			Ps	U	M	Kf						
>25	100	100	100	100	100	100	100	100	100	100	100	100
25	82.6	84.4	92	62.5	97.1	93.5	93.0	84	94.9	95.1	95.1	95.1
12.5	76.5	73.3	87	31.6	93.3	87.0	93	81	93	91.5	91.5	91.5
-----												
6.2	70.4	50	79	19.3	88.5	84.9	91	75	83.3	86.7	86.7	86.7
3.1	68.3	14.4	66	16.3	82.8	84.9	90	73	69.4	83.1	83.1	83.1
1.5	67.3	3.3	48	11.2	80	81.7	49.5	69	61.1	75.9	75.9	75.9
<0.78	51	3.3	24	3	65.7	69.8	19.8	64	54.1	69.8	69.8	69.8
No. Tested	98	90	100	98	102	93	101	100	82	83	83	83

G: Gentamicin; Sc: Methicillin; Ps: Oxacillin; M: Minocin; Kf: Keflin; Va: Vancomycin

Cl: Clindamycin; Vb: Vibramycin; To: Tobramycin

of blood culture per patient rose in the 1976-1977 period.

Streptococci: alpha and non-hemolytic: The recovery of streptococci increased in 1976-1977 to more than twice the rate previously observed in recent years. This is a heterogeneous group, including Lancefield groups B and D and other undifferentiated groups. The potential for invasive infection is reflected, however, in their recovery from the blood. Table 6 summarizes the antibiotic sensitivity of these organisms. Fewer than 30% of these isolates were sensitive to methicillin-gram antibiotics or gentamicin. Keflin and clindamycin were effective against fewer than half of the strains, while the most effective antibiotics were vancomycin, minocin, vibramycin and tobramycin. The absence of cross relationship in sensitivity to aminoglycosides is illustrated by this spectrum.

Pseudomonas aeruginosa: This ubiquitous opportunistic pathogen has continued as a conspicuous part of the flora in burn sepsis, as is shown by the large number of blood stream isolates tested for MIC in 1976-1977. Although classic burn wound sepsis was effectively controlled by topical therapy in 1964 (3), the organism repeatedly appears in blood culture, especially in gravely ill patients. The species is classically highly resistant to antibiotics, and in the 1976-1977 period, this situation is reflected in the proportion of resistant strains recognized (Table 7). Gentamicin, long a mainstay of anti-pseudomonas therapy, was effective against only 19% of strains. Kanamycin and Keflin were ineffective. Minocin was relatively effective in vitro, as were vibramycin and tobramycin. The most active antibiotic, amikacin, was introduced beginning in 1977. It and colymycin are the two most potent antibiotics in the test set. The differences in potential activity of antibiotics, whose activity differs even though the cut-off of sensitivity may be similar, is illustrated in the comparative behavior of minocin, tobramycin and vibramycin. Minocin inhibits 58.9% of strains tested, and vibramycin 43.6%, at 12.5 ug/ml, but at the next lower dilution, activity is slight. Tobramycin inhibits 11.6% of strains at 12.5 ug/ml, but is active well below the minimum test level of 1.56 ug/ml. Behavior of amikacin, colymycin and carbenicillin follow this same pattern, and the most promising antibiotics for anti-pseudomonal activity are tobramycin, amikacin, minocin, colymycin and carbenicillin. The armamentarium for this dangerous organism has been strengthened especially by the capabilities of amikacin.

It is pertinent to review the recent behavior of Ps. aeruginosa against antibiotics that have been tested over several years. Table 8 summarizes this information. Gentamicin, initially a promising drug for Pseudomonas, retained a high level of activity through 1973, but the proportion of strains sensitive

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3. Lindberg RB, Moncrief JA, Mason AD, Jr: Control of experimental and clinical burn wound sepsis by topical application of sulfamylon compounds. Ann NY Acad Sci. 150: 950, Art. 3 (Aug 14) 1968.



Table 6. Alpha- and Non-Hemolytic Streptococci: Cumulative Inhibitory Levels for 45 Strains: 1976-1977 (Jan-Sep)

Antibiotic Level ug/ml	G	Sc	Antibiotic and Per Cent Inhibited					Va	Cl	Vb	To
			Ps	U	M	Kf					
>25	100	100	100	100	100	100	100	100	100	100	100
25	34.1	30.2	71.4	30.2	100	85	95.4	78	100	82.3	
12.5	26.8	30.2	57.1	23.2	90.2	50	95.4	73.1	96.7	79.4	
-----											
6.2	24.3	20.9	28.5	23.2	80.4	37.5	95.4	46.3	74.1	78.4	
3.1	21.9	13.9	16.6	11.6	63.4	35	88.6	31.7	58.0	79.4	
1.5	14.6	13.9	16.6	11.6	53.6	27.5	54.5	31.7	54.8	67.6	
<0.78	12.1	11.6	16.6	9.3	53.6	22.5	29.5	31.7	48.3	47	
No. Tested	41	43	42	43	41	40	44	41	31	34	

G: Gentamicin; Sc: Methicillin; Ps: Oxacillin; M: Minocin; Kf: Keflin; Va: Vancomycin;

Cl: Clindamycin; Vb: Vibramycin; To: Tobramycin

Table 7. *Pseudomonas aeruginosa*: Cumulative Inhibitory Levels for  
185 Strains from Blood Cultures. 1976-1977 (Jan-Sep)

Conc. ug/ml	C	M	K	Antibiotic and Per Cent Inhibited				Co	Conc. ug/ml	Cb
				Kf	To	Vb	Ak			
> 25	100	100	100	100	100	100	100	100	>1250	100
25	26.7	85.4	19.1	5.6	80.2	70.4	98.3	89.3	1250	92.7
-----										
12.5	19.1	58.9	7.3	3.9	61.6	43.6	98.3	89.3	625	90.5
6.2	4.9	17.2	3.3	2.8	55.8	13.3	85.2	87.6	312	86.9
-----										
3.1	2.7	3.7	1.1	2.8	55.2	5.6	67.9	82.5	156	58.6
1.56	0.5	1.1	0.6	1.6	54.6	4.9	37.7	68.5	78	51.4
<0.78	0.5	1.1	0.6	0.6	47.0	4.2	6.5	43.2	39	24.6
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has fallen steadily since that time. At 19% of isolates sensitive, its status is doubtful. Minocin has shown, from an earlier low level of activity, a marked rise in the proportion of strains sensitive in the past 19 months. Colymycin has continually been the most effective drug, *in vitro*, against *Pseudomonas*. Carbenicillin was, six years ago, only moderately active *in vitro* against septicemic strains of *Ps.aeruginosa*. This activity rose sharply in 1973, and although some loss has occurred, it is still effective against three-fifths of these isolates.

Table 8. Comparative Sensitivity of *Pseudomonas aeruginosa* Against 4 Antibiotics

Antibiotic	Year and Per Cent of Strains Inhibited by 12.5 ug/ml						
	1970	1971	1972	1973	1974	1975	1976-1977
Gentamicin	71.6	71.4	68.0	84.3	61.8	40.0	19.1
Minocin	-	-	-	31.3	15.7	16.8	58.9
Colymycin	63.4	73.3	70.0	86.2	93.3	86.3	89.3
Carbenicillin (Inhibitory level: 312 ug/ml)	33.9	30.0	34.6	80.4	70.8	68.8	58.6

Klebsiella pneumoniae: *Kleb. pneumoniae* remains numerically a major cause of septicemia in burned patients, and the outcome in patients with this form of bacteremia has not been one to view with satisfaction. Table 9 shows the antibiogram pattern with 175 septicemic strains. The older antibiotics, gentamicin, kanamycin, and Keflin were virtually ineffective, as they have been for the past 3 years. Minocin showed, as it has since its first testing in 1973, a high level of effectiveness at upper dosage limits. Tobramycin, first used in 1975, was effective against one-third of strains tested; the strains tobramycin-resistant were highly resistant. Vibramycin and the new antibiotic, amikacin, were highly effective, as was colymycin. The armamentarium available for control of *Klebsiella* sepsis has been broadened encouragingly with the addition of tobramycin and amikacin, but control of clinical burn sepsis due to *Klebsiella* remains a grave problem.

Enterobacter cloacae: This species has in previous years (especially 1974) exhibited potential for establishing a major epidemic in the burn ward. During 1976-1977, it was not present on this scale, but 41 septicemic strains were collected. Sensitivity is summarized in Table 10. As with other Enterobacteriaceae, this is a species whose presence in blood often connotes a grave prognosis. The spectrum of sensitivity and the indication for appropriate antibiotics *in vitro*, closely parallels that observed with *Kleb. pneumoniae*. Gentamicin, kantrex and Keflin were ineffective. Minocin, tobramycin,

Table 9. *Klebsiella pneumoniae*: Cumulative Inhibitory Levels for 175 Strains from Blood Cultures, 1976-1977 (Jan-Sep)

Conc. ug/ml	G	M	K	Antibiotic and Per Cent Inhibited				Co
				Kf	To	Vb	Ak*	
25	100	100	100	100	100	100	100	100
25	8.6	98.2	2.9	14.2	38.8	98.1	90.9	88
12.5	7.4	95.2	2.3	9.7	37.1	93.0	90.9	88
6.2	4.0	16.9	1.1	5.1	34.2	89.9	45.4	88
3.1	3.4	47.6	1.1	2.8	34.2	79.2	40.9	87.4
1.5	2.2	2.3	0.6	1.7	33.7	27.0	0	80.0
<0.78	0	0	0	1.7	29.1	3.1	0	68.0
Total Tested	174	168	169	175	175	159	22	175

G: Gentamicin; M: Minocin; K: Kantrex; Kf: Keflin; To: Tobramycin;

Vb: Vibramycin; Ak: Amikacin; Co: Colistin

\* Amikacin started in 1977; hence only 22 strains tested.



Table 10. Enterobacter cloacae: Cumulative Inhibitory Levels for  
41 Strains from Blood Cultures. 1976-1977 (Jan-Sep)

Conc. ug/ml	G	M	Antibiotic and Per Cent Inhibited				Ak*	Co
			K	Kf	To	Vb		
> 25	100	100	100	100	100	100	100	100
25	17	97.5	2.5	31.2	90.2	97.1	100	94.8
-----								
12.5	14.6	87.5	2.5	15.6	82.9	94.2	95	94.8
6.25	12.1	80	2.5	15.6	82.9	88.5	95	92.3
3.12	12.1	47.5	0	15.6	82.9	68.5	70	92.3
1.56	4.8	7.5	0	12.5	82.9	17.1	1.0	87.1
< 0.78	2.4	2.5	0	0	73.1	0	0.5	76.9
No. Tested	41	40	40	32	41	35	20	39

G: Gentamicin; M: Minocin; K: Kantrex; Kf: Keflin; To: Tobramycin;

Vb: Vibramycin; Ak: Amikacin; Co: Collistin

\* Amikacin used only in 1977.

vibramycin, amikacin, and colymycin were highly active in vitro. Again, the newer antibiotics are most encouraging as potential agents for control of infection with this dangerous opportunist.

Escherichia coli and Proteus mirabilis: These species are presented together since they represent a minority of Enterobacteriaceae causing septicemia. This low recovery rate does not detract from their importance to individual patients, nor is there any assurance that, in view of the epidemic potential of other species of this group, especially Providencia, Klebsiella and Enterobacter, that these species may not, without warning, become a major part of the nosocomial infection problem. Table 11 presents in abbreviated form the sensitivity data for each of these species. Proteus mirabilis showed all antibiotics except vibramycin and colymycin to be active to a significant degree at the 12.5 ug/ml level. When lower dilution results were considered, the most promising antibiotics were gentamicin, kanamycin, Keflin, tobramycin and amikacin. Tobramycin was by far the most active antibiotic against Proteus mirabilis.

E. coli was inhibited in 40 to 55% of strains by gentamicin, kantrex, Keflin, and vibramycin. Seventy to 80% of the 34 strains tested were inhibited by minocin, tobramycin, amikacin and colymycin. The antibiogram spectrum of the E. coli strains recovered suggested that these were the most heterogeneous strains of any of the opportunistic pathogens collected from burn patients. The most promising antibiotics on the basis of this series were tobramycin and colymycin.

Infrequent Enterobacteriaceae: Four additional species of Enterobacteriaceae: Serratia marcescens, Citrobacter freundii, Klebsiella ozoenae and Enterobacter agglomerans were recovered from blood during 1976-1977. The numbers were small: 14 strains of S. marcescens; 15 of C. freundii; 2 of K. ozoenae and 2 of E. agglomerans. S. marcescens strains were highly sensitive to minocin and vibramycin (100%), 70% sensitive to kantrex and 40-50% sensitive to gentamicin, Keflin and colymycin. Organisms recovered from individual episodes of Serratia sepsis on the burn ward varied in antibiograms.

Citrobacter freundii strains were all (17) sensitive to minocin, tobramycin, amikacin and colymycin. Seventeen per cent of strains were sensitive to gentamicin and to kantrex. All were resistant to Keflin.

## DISCUSSION

During the interval of 1976-1977, major septicemic bacterial species included Staph. aureus, Ps. aeruginosa and Kleb. pneumoniae. Numerically significant numbers of Staph. epidermidis and a mixed population of streptococci were recovered, but these strains did not appear to be associated with severe clinical illness. Entero. cloacae and E. coli were recovered from a smaller proportion of patients with bacteremia, but as with

Table 11. Proteus mirabilis and Escherichia coli: Cumulative Inhibitory Levels for Strains from Blood Cultures 1976-1977 (Jan-Sep)

Conc. ug/ml	G	M	K	Antibiotic and Per Cent Inhibited			
				Kf	To	Vb	Co
<u>Proteus mirabilis</u>							
25	83.3	88.8	63.3	62.0	95.6	23.5	100
12.5	70.8	62.9	63.3	48.2	95.6	5.8	100
6.25	70.8	11.1	56.6	17.2	95.6	0	87.5
3.1	41.6	7.4	43.3	0	86.9	0	62.5
<u>Escherichia coli</u>							
25	63.6	96.7	57.5	63.6	81.8	84.2	90.0
12.5	51.5	74.1	54.5	57.5	78.7	42.1	70.0
6.25	30.3	64.5	45.4	33.3	75.7	31.5	25.0
3.1	18.1	58.0	18.1	18.1	72.7	31.5	0.5

G: Gentamicin; M: Minocin; K: Kantrex; Kf: Keflin; To: Tobramycin;

Vb: Vibramycin; Ak: Amikacin; Co: Colistin

\* Amikacin started in 1977.

other species of the Enterobacteriaceae, they were frequently associated with fatal sepsis. Selection of optimal antibiotic therapy on the basis of recent experience remained a valid hypothesis. The fall, rise, and subsequent fall in methicillin-group activity with staphylococci emphasizes the importance of frequent and continuing review of susceptibility patterns of this labile population. Currently minocin, Keflin and vancomycin would appear to be the optimal antibiotics for staphylococcal infection on the basis of in vitro data.

Among gram-negative opportunistic invasive bacteria, new antibiotics of promise in vitro include primarily amikacin and tobramycin. Minocin has resumed a level of effectiveness beyond that seen in recent years, but gentamicin has fallen markedly in potential effectiveness. Carbenicillin retains a potential activity for 60% of isolates tested; this antibiotic is today more effective against *Pseudomonas* than it was 5 years ago.

Kleb. pneumoniae, numerically a major part of the septicemia picture during this period, was markedly susceptible to minocin, vibramycin, amikacin and colymycin. It was virtually resistant to gentamicin, Keflin, kantrex, and in two-thirds of strains to tobramycin. As with all Enterobacteriaceae, resistance transfer factors are common, and control of *Klebsiella* in a burn ward is far from a foregone conclusion.

The reaction pattern for septicemic strains of Entero. cloacae was similar to that of Kleb. pneumoniae. In addition, the strains were over 80% sensitive to tobramycin. This species was relatively uncommon over 1976 and 1977, but its reappearance remains a possibility at any time.

Minor species of Enterobacteriaceae including S. marcescens, Proteus mirabilis, E. coli and Citro. freundii exhibited species distinctive antibiotics. These strains can be lethal when invasive; their numerical level offers no assurance against epidemic spread in the future, and isolates will be monitored against this possibility. The newer agents, tobramycin, vibramycin and amikacin have improved the prospects for effective antibiotic therapy against opportunistic gram-negative invading bacteria.

#### PRESENTATIONS

Lindberg RB: Antibiotic surveillance in intensive care wards. Symposium on Nosocomial Infections. Houston, Texas. Nov. 10-12, 1976.

#### PUBLICATIONS

None



ANNUAL PROGRESS REPORT

PROJECT NO. 3S762774A820-00, MILITARY BURN TECHNOLOGY

REPORT TITLE: STUDIES OF INFECTION AND MICROBIOLOGIC SURVEILLANCE  
OF TROOPS WITH THERMAL INJURY -- BACTERIOPHAGE  
TYPES OF PSEUDOMONAS AERUGINOSA FOUND IN BURNED  
SOLDIERS

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## ABSTRACT

PROJECT NO. 3S762774A820-00, MILITARY BURN TECHNOLOGY

REPORT TITLE: STUDIES OF INFECTION AND MICROBIOLOGIC SURVEILLANCE  
OF TROOPS WITH THERMAL INJURY -- BACTERIOPHAGE  
TYPES OF PSEUDOMONAS AERUGINOSA FOUND IN BURNED  
SOLDIERS

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Period covered in this report: 1 October 1976 - 30 September 1977

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In search for simpler methods to achieve the strain differentiation that the Institute of Surgical Research's Pseudomonas phage typing system has provided, the recently introduced serotyping system, produced by Difco, Inc, was tested. Out of a total of 525 strains collected over a 14-month period, a total of 12 serotypes were recognized. Specificity was high; fewer than 3% of strains were rough or non-reacting. Epidemic types could be recognized and a chronic low-grade epidemic with type 4 in the burn ward was followed, after 12 months, by an intense explosive epidemic due to type 15. Chronologic sequencing showed that the system could distinguish epidemic groups but it was not as sensitive as phage typing. Important differences in virulence and therapeutic response could be detected by phage typing but not by serotyping. Combination of the simple serotype with the sensitive and precise phage typing system is suggested as the direction to follow in this study.

Pseudomonas  
Serotype  
Phage type  
Humans  
Infection

## STUDIES OF INFECTION AND MICROBIOLOGIC SURVEILLANCE OF TROOPS WITH THERMAL INJURY -- BACTERIOPHAGE TYPES OF PSEUDOMONAS AERUGINOSA FOUND IN BURNED SOLDIERS

Pseudomonas aeruginosa has been able to persist as a major cause of nosocomial infections despite the development of a succession of antimicrobial agents to which it is susceptible in vitro. The species has at any given time, shown a high level of antibiotic resistance and as an opportunistic invader, it is of greatest clinical importance in populations with less than optimal defense mechanisms: the aged, the very young, the severely traumatized and the immunologically deficient. An essential part of any program directed toward control of Ps. aeruginosa in hospital populations is a means of recognizing strains in an infected population. The organism is capable of rapid epidemic spread, and specific strain identification is needed if one is to understand an infection problem when it exists as well as to evaluate the effectiveness of control measures when they are applied. Out of all hospital populations, burned patients constitute one of the most seriously threatened groups as far as Pseudomonas colonization, infection, and sepsis are concerned.

In the Institute of Surgical Research an ongoing program to develop a phage typing system for differentiation of Ps. aeruginosa strains was begun in 1961 and applied to the bacterial population of the burn ward. The system developed was highly effective, and the typing set was distributed to investigators throughout the world. It was, as is the case with phage typing technic, a demanding and difficult procedure, well suited to research on Pseudomonas epidemiology but requiring a high level of expertise to maintain. Personnel changes in 1976 facilitated a survey of other methods for achieving epidemiologic results which might parallel those achieved with the ISR Pseudomonas phage typing system. The concurrent appearance of a commercial serologic typing set of antisera selected by an international committee on Pseudomonas typing permitted assessment of that approach to strain differentiation of Ps. aeruginosa. The phage typing approach offers a refined detailed result which most completely separates strains, but if an adequate grouping of epidemic strains can be achieved with a simpler serologic approach, it merits consideration. The objective of any typing system is the reliable differentiation of strains by whatever means are utilized.

### MATERIALS AND METHOD

The phage typing system has been described in detail (1). The serologic system employed represents a consensus of the International Panel of the Subcommittee on Pseudomonadaceae of the International Committee on Systemic Bacteriology. This committee included Drs. T. Bergan, I. Duncan,

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1. Lindberg RB, Latta RL: Phage typing of Pseudomonas aeruginosa: Clinical and epidemiologic considerations. J Infect Dis 130: 533-542, 1974.

J. Homma, P.V. Liu, E. Meitert, M.T. Parker and M. Veron. The serologic system was based chiefly on Habs' cultures 1-12 as used by Verder, with additional strains from Vernon, Verder, Lanyi and Meitert. The antisera were prepared from autoclaved antigens. Seventeen "types" were proposed. Whether these entities are properly designated as serotypes or serogroups will be the subject of future study, but the present the term serotype will be used. Typing is performed with live or autoclaved suspensions of the bacteria in question. There appear to be few strains in the series we have typed in which thermolabile locking factors were present, and the convenience of typing live suspensions prompted use of this technic wherever possible. The sera were obtained from Difco, Inc., Detroit, Michigan.

## RESULTS

One hundred thirty-one strains of *Ps. aeruginosa* from clinical specimens were collected in 1976, and 394 in 1977. These were typed with the full 17-factor set, using slide agglutination and live antigens followed up when indicated by autoclaved suspensions. The type distribution is shown in Table 1. There were 13 types, plus a small group of non-typable strains observed. Five types were present in 1976, and with the larger sample, 9 types in 1977.

Table 1. Serotypes of *Pseudomonas aeruginosa* from Burn Patients, ISR, 1976-1977

Type	1976	No. of Strains and % of Total		% of Total
		% of Total	1977	
1,9	0		2	
2,3,6,15	0		3	
4	60	45.8	110	27.9
4,9	7		0	
4,9,10	14	10.6	20	5.0
7	0		3	
8	0		2	
9	0		2	
9,10	0		3	
11	23	17.5	0	
14	0		7	
15	27	20.6	239	60.6
Non-typable	0		3	
Total strains typed	131		394	

Only 4 types were found in significant numbers; the remaining 9 types were not present in more than 3 strains each. In 1976, type 4 was predominant at 45.8% of all strains tested. Its incidence dropped to 27.9% in 1977. Type 15 was numerically significant in 1976; in 1977 it made up



60.6% of all strains, and was frequently overwhelmingly predominant in given time intervals. Type 4 remained numerically prominent in 1977, but only one other type, 4,9,10, appeared in significant numbers. As a means of identifying the presence of epidemic strains, serotyping was effective.

The correspondence of phage types and serotypes is under study, but a definitive answer is not yet available. Phage types included diverse serotypes in some degree. Table 2 shows three serotypes each including 2 or 3 phage types. This does not represent an exhaustive survey, but does indicate the variation possible within a given serotype. The predominant sera type 15 was the most frequently encountered in these phage types, but this preponderance may simply indicate that the type 15 strains were most numerous at the time the observation was made.

Table 2. Individual Phage Types of Pseudomonas aeruginosa with Different Serotypes

Phage Type	Serotype	No. of Strains
24	4	3
	4,9,10	2
	NT	2
1214	4	1
	15	6
	4,9,10	2
	11	1
24,44,1214,68	15	6
	4,9,10	1

The opposite question was also raised: within a given serotype are there multiple phage types? Here the result was more clearcut. Each serotype included more than one phage type (Table 3). Each group of strains which fell into one serotype included a majority of strains of a single phage type. Thus, with serotype 4, phage type 24 was the most common type. Serotype 15 included mainly strains of phage type 21,24,44,12,14,68. There were two other phage types included in each of these serotypes. In addition, further trials showed that a given phage type might appear in two serotypes. This cross reaction capability does not appear to invalidate the major epidemiologic conclusion that an epidemic outbreak can be characterized by a single serotype.

In epidemiologic studies using phage type as the differentiating criterion, patients in whom septicemia occurred were studied more closely. The possible presence of strains or types with a predilection for wound invasion is a matter of concern. A group of 28 patients with positive blood culture for

Table 3. Individual Serotypes of Pseudomonas aeruginosa with Different Phage Types

Serotype	Phage Type	No. of Strains
4	21, 31, 68	10
	(31), 68, 119X	7
	24	18
15	21, 24, 44, 1214, 68	33
	21, 68	3
	1214	2

Ps. aeruginosa was checked for the type of pseudomonad recovered. Table 4 summarizes these results. The predominant types from all sources were represented in this group. One-third of the patients were invaded with type 4 and two-thirds with type 15. These patients were from the 1977 collection: the type 4 and type 15 incidences for that group were 27.9 and 60.6%. Thus, as had been observed with phage typing, the incidence of serotypes in the blood essentially reflected the overall incidence of Ps. aeruginosa types. The indication with serotyping as with phage typing is that the septicemic strains are a reflection of type distribution of the whole population, not a selected group of strains of especial virulence.

Table 4. Serotype of Pseudomonas aeruginosa from Blood of 28 Patients with Bacteremia

Serotype	No. of Patients	No. of Strains
4	10*	13
15	20	35
NT	2	2

\* Two patients yielded cultures from which type 4 was recovered followed by cultures (time interval up to 30 days) from which type 15 was recovered. Two patients yielded both type 15 and non-typable strains.

The chronologic distribution of phage types offers a picture of the cross-infection pattern, and the dynamics of strain transfer among patients, in the burn ward. This information is obscured when the predominant type is summarized on an annual basis. The data for the months available are presented in Table 5. May-July and October - December 1976 are shown, together with January - June 1977. During 1976, type 4 was predominant in May, June, November and December. Type 11 showed a sharp peak of numbers in July,

Table 5. Monthly Distribution of Predominant *Pseudomonas aeruginosa* Serotypes in ISR Burn Patients, 1976-1977

Serotype	Year and Month												Total Strains			
	May	Jun	Jul	1976 ---			Oct	Nov	Dec	Jan	Feb	1977 Mar Apr		May	Jun	
1, 9															2	2
2, 3, 6, 15															3	3
4	9	11	8					12	19	18	16	3	7	43	22	168
4, 9		6														6
4, 9, 10		7	9									10	8	2		36
7															3	3
8											3					3
9															4	4
9, 10														2		2
11			16				6	2								24
14														7		7
15	4		3				14		7	6			114	115		263
NT												1	1	1		3
Strains/ Month	13	24	36	20	14	26	24	19	14	16	169	149				524

but was not seen again after November. Type 15 was present in small numbers during 4 months, but was predominant only in October. During the months observed in 1976, no clearcut epidemic pattern was seen, although type 4 came closest to this category. In January and February of 1977, type 4 was present in numbers similar to those seen in 1976. Type 4,9,10 was the most common in March and April. In May and June, an abrupt appearance of type 15 on epidemic scale overshadowed all other types present. More strains were tested in those months, and a more valid picture of the pattern of strain distribution was obtained, but the major population was type 15. Type 4 was present as 25% of all strains in May, in contrast to January when 75% of isolates were type 4. Type 15 made up 67% of all isolates in May, and 77.1% in June. The pattern was one of a major epidemic episode with a minor rise of an established type occurring.

## DISCUSSION

The problem of "finger-printing" epidemic and inter-epidemic strains of *Ps. aeruginosa* in a burn ward had been solved with a comprehensive but technically difficult preparation of a phage typing system. With the need to continue this surveillance complicated by loss of personnel highly expert in phage research, evaluation of the proposed commercially available serotyping system was undertaken. It is evident that a picture of strain distribution similar to that obtained with phage typing could be obtained with the serotyping system. When the identities of phage types and serotypes were compared, the two did not correspond. A given phage type may include strains varying in serotype, and a serotype may include more than one phage type. However, the overall pattern of chronic colonization of the burn ward by certain types, with the possibility of other types appearing as overwhelming epidemic strains is similar to the pattern which phage typing revealed. The distinctions are not as fine nor as clearcut as in the case with phage typing, but the information was useful for recognizing epidemic and interepidemic periods.

There are specific details in strain identity related to virulence that would not be detected by serotyping. An example is the experience with strains recovered December 1972 through May 1973. In all, over 104 isolates from 25 patients were recovered. The strain A-71 had a phage type 2,7,21,24,44,68,352,119X,F7,M4. It was uniquely virulent for burned rats; kills occurred within 72 hours of seeding, and topical therapy saved none. A less variant, naturally occurring, was detected by colony morphology. This strain, A-71-#2, had the formula 2,7,21,24,68,F7,M4. It was highly virulent but rats treated with Sulfamylon survived. Variant A-71#3 was yet simpler: its formula was 2,7,21,68,F7. This form was non-virulent. This discovery bears within it the possibility of detecting a plasmid-mediated virulence factor, a hitherto unknown phenomenon. With serotyping, these strains would not have been detected.

Projected further studies involve serotyping as a recognition technic, with further detailed differentiation of epidemic strains as they emerge. With such an approach, the A-71 phenomenon would have been detected. The sero-



typing-phage typing systems together offer an improved approach to studying *Pseudomonas* epidemiology in burn wards.

PRESENTATIONS AND/OR PUBLICATIONS

None

ANNUAL PROGRESS REPORT

PROJECT NO. 3S762774A820-00, MILITARY BURN TECHNOLOGY

REPORT TITLE: STUDIES OF INFECTION AND MICROBIOLOGIC SURVEILLANCE  
OF TROOPS WITH THERMAL INJURY -- PATHOGENESIS OF  
BURN WOUND INFECTION: BACTERIAL FLORA OF WOUNDS OF  
MILITARY PERSONNEL RECEIVING TREATMENT WITH  
SULFAMYLDON OR SILVER SULFADIAZINE

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1 October 1976 - 30 September 1977

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## ABSTRACT

PROJECT NO. 3S627774A820-00 MILITARY BURN TECHNOLOGY

REPORT TITLE: STUDIES OF INFECTION AND MICROBIOLOGIC SURVEILLANCE  
OF TROOPS WITH THERMAL INJURY -- PATHOGENESIS OF  
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Bacterial infection, local and systemic, remains the principal cause of death in severe burns. Major species involved are Staphylococcus aureus, Klebsiella pneumoniae, Pseudomonas aeruginosa, Escherichia coli, Enterobacter cloacae and Proteus mirabilis. An epidemic pattern, with periods of peak predominance of a given species interspersed with incursion of other species, typified the burn ward during 1976-1977. Kleb. pneumoniae, Ps. aeruginosa and Staph. aureus were the pathogens most frequently involved in sepsis. E. coli and Proteus mirabilis were more frequent in sepsis than had previously been observed, while a recent major pathogen, Providencia stuartii, had entirely disappeared. Detailed taxonomic effort showed that uncommon enteric forms such as Citrobacter freundii caused lethal sepsis, as did species of Pseudomonas other than aeruginosa. Continued detailed monitoring offers the only valid means of recognizing the role of nosocomial flora in burn wound infection. There is no apparent limit to the potential for opportunistic invasion by bacteria customarily regarded as normal flora.

Burns  
Klebsiella  
Staphylococcus  
Pseudomonas  
Sepsis  
Humans

STUDIES OF INFECTION AND MICROBIOLOGIC SURVEILLANCE OF TROOPS  
WITH THERMAL INJURY -- PATHOGENESIS OF BURN WOUND INFECTION:  
BACTERIAL FLORA OF WOUNDS OF MILITARY PERSONNEL RECEIVING  
TREATMENT WITH SULFAMYLON OR SILVER SULFADIAZINE

Bacterial infection remains the major factor in morbidity of severely burned patients, as it has for several decades. Although the extent of burn that is compatible with survival has been increased, infection remains the principal cause of death in patients who survive the period of resuscitation. Topical chemotherapy is an essential component in burn treatment, but opportunistic pathogens have made control of wound bacteria more difficult than was the case when such therapy was introduced in 1964. The classical burn wound invader, Pseudomonas aeruginosa, has for long periods been held to a minimal role as an invading species, but this form still recurs in epidemics of new strains which colonize the burn ward population. More prolonged epidemic periods with Enterobacteriaceae species recur, with a range, since 1968, to include Providencia stuartii, Enterobacter cloacae, Klebsiella pneumoniae, and possibly Proteus mirabilis. Antimicrobial resistance to topical agents among these species is relatively common. Septic shock following bacterial proliferation in tissues of the severely burned patient is frequently seen. A precise delineation of the offending microbial flora and detection of long-term trends by comparison of successive years' findings furnishes a basis for understanding the pathogenesis of burn sepsis and for projecting therapy even before specific information from individual cultures is available. Microbiological monitoring also permits the recognition of new invasive strains even of species not generally recognized as capable of invasive proliferation in wounds.

ANTEMORTEM BACTERIOLOGY OF BURN PATIENTS - 1976-1977

In previous summaries the bacterial flora for 12 month intervals was analyzed. However, the change in reporting period introduced in 1976 presented an additional 9 months of data in 1977, which is included in this resume. The total bacterial and yeast strains isolated from 7 major sites is summarized in Table 1. There were 443 patients admitted during the reporting interval, but of these 72 had no cultures taken. These are omitted from this summary. A trend toward increased collection of "routine" blood cultures, drawn whether or not the patient showed clinical indications of potential sepsis, has been observed during the past 2 years. Thus, in 1975 an average of 274 blood culture specimens were collected per month. The 1976-1977 average per month was 531. In 1975, 47.8% of all cultures taken were blood cultures. In 1976-1977, this proportion rose to 75%. Sputum samples yielded the most isolates, with wound cultures second in number of strains recovered. Staphylococcus aureus was the organism most often recovered, with Ps. aeruginosa close in total recoveries. Kleb. pneumoniae and Enterob. cloacae were the next most frequently encountered species, with significant numbers of Escherichia coli and of Proteus mirabilis also recovered. Enterob. cloacae was relatively scarce in the latter half of 1975, but resumed its role as a major opportunistic species in colonizing burn patients in 1976.



Table 1. Antemortem Bacteriology of Burn Patients, 1 Jan 1976 - 30 September 1977

Organism	Source and Number of Isolates							Total Isolates
	Wound Surface	Blood	Sputum Lukens	Urine	I.V.Cath. Tip	Foley Cath. Tip	Biopsy	
Staph. aureus	226	260	350	54	72	8	64	1034
epidermidis	57	91	179	94	17	12	22	472
Alpha Strep. not D	39	4	357	7	0	0	3	410
Non-Hemol. Strep. not D	24	8	87	27	10	7	6	169
Beta-Hemol. Strep. not A,B,D	5	0	16	3	0	2	1	27
Strep. Group B	0	0	5	0	0	0	0	5
Strep. Group D not Enterococci	5	18	25	0	0	0	1	49
Group D. Enterococci	6	21	10	16	1	1	6	61
Strep. pneumoniae	0	3	26	0	0	0	0	29
Bacillus sp.	12	7	11	11	1	1	10	44
Corynebacterium sp.	0	3	0	0	0	0	0	3
Ps. aeruginosa	218	182	453	199	64	18	104	1238
Pseudomonas sp.	33	14	48	15	16	10	22	158
Kleb. pneumoniae	64	145	227	137	40	15	53	681
Klebsiella sp.	21	39	48	35	23	0	31	197
Entero. cloacae	49	43	33	45	7	2	22	201
aerogenes	4	4	7	11	0	0	2	28
agglomerans	4	0	9	8	6	0	12	41
E. coli	45	34	72	95	6	9	12	273
Serratia marcescens	8	17	33	16	1	1	4	80
Proteus mirabilis	61	29	130	78	3	13	11	325
morganii	15	4	20	15	0	0	0	54
rettgerii	2	0	3	4	0	0	0	9
vulgaris	1	0	1	0	0	0	0	2
Prov. stuartii	0	0	1	0	0	0	0	1
Citro. freundii	5	12	8	5	3	1	5	39
diversus	1	2	1	1	0	0	0	5
Flavobacterium sp.	1	0	1	1	0	0	0	3
Acineto. calcoaceticus	1	0	2	1	0	0	1	5
Aeromonas sp.	1	0	1	0	0	0	0	2
Micrococcus sp.	0	12	4	1	2	0	1	20
Neisseria sp.	3	0	21	0	0	1	0	25
Candida sp.	39	42	50	162	15	6	11	325
No. Patients Cultured:	207	355	210	258	130	72	113	
No. Specimens:	663	11158	996	1220	282	90		
Total Isolates:	6015							
Total Specimens:	14099							
Total patients on whom at least one culture was done:	380							

Serratia marcescens decreased in incidence from the preceding year. A species conspicuous by its absence, in contrast to preceding years, was Providencia stuartii. One strain was isolated from a sputum specimen. While it was scarcely common in 1975, in 1973 it was the most common gram-negative species, with 873 strains isolated.

The total isolates recovered do not reflect the incidence in terms of patients. Table 2 presents the species recovered in terms of the number of patients positive in relation to the number of patients cultured. The most common species on the burn wound was Staph. aureus, followed by Ps. aeruginosa and Kleb. pneumoniae. These species, in that order, were most often recovered in blood culture as well.

#### BURN WOUND BACTERIOLOGY

Although several species of Enterobacteriaceae have been recovered from burn tissues of patients with lethal wound sepsis, unequivocal burn wound sepsis has only been reproduced in animals with Ps. aeruginosa. However, the burn wound flora is an integral part of the wound sepsis problem in burn patients, and the frequency with which the major species occur in the burn is shown in Table 3. Staph. aureus was the most frequently recovered species, over half of the patients had wounds positive for this organism. Staphylococcus epidermidis was present in 20% of patients, and alpha-hemolytic and non-hemolytic streptococci were found on 27% of patients. In contrast to previous years, no Group A streptococci were recovered from wounds or other sources. These streptococci have not been implicated in burn wound infection.

Ps. aeruginosa was the second most common species, although it was far less common than in 1975 when it was found on 57% of patients. Kleb. pneumoniae, on 30% of burn patients, was the other principal gram-negative species on the burn wound. Here too, the proportion of burn patients positive was lower than the 47% observed in 1975. Enterocloacae, E. coli and Proteus mirabilis were the remaining species found on at least 10% of patients cultured. The overall picture which emerged was one in which all species of gram-negative bacteria were less frequently recovered than had been the case a year earlier.

#### RESPIRATORY TRACT FLORA IN BURNS

Pulmonary complications are a common and often lethal part of the infection problem in the severely burned patient. There were 210 patients from whom sputum or Lukens tube cultures were obtained. Principal species recovered from this sampling are shown in Table 4. The most frequent pathogenic species was Staph. aureus; the percentage of patients positive has, for several years, ranged between 50% and 60%. The high incidence of streptococci was not previously recorded but is ascribed to a more detailed culture technic now being employed in the diagnostic laboratory. Among the principal species of gram-negative bacilli, Kleb. pneumoniae, in 43.6% of patients,

Table 2. Antemortem Bacteriology of Burn Patients: 1 January 1976 - 30 September 1977

Organism	Source and Number of Patients Positive in Culture						
	Wound	Blood	Sputum Lukens	Urine	I.V. Cath. Tip	Foley Cath Tip	Biopsy
<i>Staph. aureus</i>	107	92	113	49	45	8	46
epidermidis	43	60	95	67	14	12	16
Alpha-Strep. not D	32	4	149	7	8	7	3
Non-hemol. Strep. not D	21	8	52	23	0	0	5
Beta-hemol. Strep. not A, B, D	5	0	9	2	0	2	1
Group B Strep.	0	0	3	0	0	0	0
Group D Strep., not Enteroc.	4	6	17	0	0	0	1
Group D Strep. Enterococcus	6	9	7	13	1	1	2
<i>Strep. pneumoniae</i>	0	2	6	0	0	0	0
<i>Bacillus</i> sp.	12	7	11	11	1	1	16
<i>Corynebacterium</i> sp.	0	3	0	0	0	0	0
<i>Ps. aeruginosa</i>	81	72	111	69	35	17	53
<i>Pseudomonas</i> sp.	24	9	29	10	15	9	14
<i>Kleb. pneumoniae</i>	49	62	81	73	25	12	25
<i>Klebsiella</i> sp.	13	19	29	21	14	0	19
<i>E. coli</i>	35	26	50	54	6	8	8
<i>Enterocloacae</i>	28	27	23	28	7	2	10
aerogenes	3	0	6	9	0	0	0
agglomerans	0	0	7	7	5	0	8
<i>Serratia marcescens</i>	8	10	18	14	1	1	4
<i>Proteus mirabilis</i>	30	16	37	54	3	10	9
morganii	4	2	5	37	0	0	0
rettgerii	2	0	1	6	0	0	0
vulgaris	1	0	1	0	0	0	0
<i>Providencia stuartii</i>	0	0	1	0	0	0	0
<i>Citro. freundii</i>	5	7	6	54	2	1	3
diversus	1	2	1	5	0	0	0
<i>Flavobacterium</i> sp.	1	0	1	1	0	0	0
<i>Acineto. calcoaceticus</i>	1	0	2	1	0	0	1
<i>Aeromonas</i> sp.	0	0	1	0	0	0	0
<i>Neisseria</i> sp.	1	0	21	0	0	0	0
<i>Micrococcus</i> sp.	0	8	4	1	2	0	1
<i>Candida</i> sp.	22	13	36	3	13	6	9
Total No. Patients Sampled	207	355	210	258	130	72	113

Table 3. Predominant Burn Wound Surface Flora  
in 207 Patients - 1976-1977

Species	No. Patients Positive	No. Strains Recovered	% of Patients Positive
Staph. aureus	107	226	51.7
Staph. epidermidis	43	57	20.8
Strep. alpha-hemol. *	36	44	17.3
Strep. non-hemol	21	24	10.1
Ps. aeruginosa	81	218	39.1
Kleb. pneumoniae	62	75	30.0
E. coli	35	45	16.9
Entero. cloacae	28	49	13.5
Proteus mirabilis	30	61	14.5

\* 10 strains Strep gp D.

was less common than it had been during the past 4 years. In 1971, it was found in 45% of patients, but it was recovered from 69.2% of them in 1975. Similarly, Entero. cloacae was found in sputa of 35.7% of patients cultured in 1974, but this value fell to 17.3% in 1975. E. coli has not varied widely in the past 2 years, and Proteus mirabilis has increased in incidence in sputa from only 7.5% of patients in 1975. Ps. aeruginosa was less common in 1976-1977 than its occurrence in sputa of 65.4% of patients in 1975. It was evident that long term variations of a major order occur in the sputa of burn patients. These variations parallel changes in wound flora. The assumption that these specie changes can be correlated with changes in agents used for treatment is not entirely supported by some of these shifts, which occurred with unrecognizable alteration in treatment routines.

Table 4. Principal Species of Bacteria Recovered  
from Respiratory Tract of 210 Burned Patients, 1976-1977

Species	No. Patients Positive	No. Isolates	% of Patients Positive
Staph. aureus	113	350	53.8
Staph. epidermidis	95	195	45.2
Alpha Strep.	149	357	71.0
Strep. gp D	24	35	11.4
Non-hemol. Strep.	52	87	24.8
Ps. aeruginosa	111	453	52.9
Kleb. pneumoniae	99	475	43.6
Entero. cloacae	23	33	10.9
Proteus mirabilis	37	130	17.6



Changes in incidence of major species in sputum, a reflection of potential pathogens present in the lung, are more clearly shown in a retrospective summary. Table 5 summarizes the major species recovered since 1972. The incidence of Staph. aureus has been relatively constant. Since its low point in 1972, the recovery of Staph. aureus from the lung at autopsy has remained high. A gradual rise in incidence of Kleb. pneumoniae and of Ps. aeruginosa was reversed in 1976-1977. This change has been paralleled by a drop in rate of recovery of Kleb. pneumoniae in lungs at autopsy, but the recovery rate of Ps. aeruginosa has not fallen. Entero. cloacae has dropped to one-third of the incidence observed when this species was predominant on burn wounds. E. coli and Proteus mirabilis have appeared to fluctuate with no correlation to recovery of these species in lung at autopsy.

Table 5. Principal Species of Bacteria Recovered from Respiratory Tract of Burn Patients, 1972-1977

Species	% of Patients Exhibiting Positive Sputum on Culture				
	1972	1973	1974	1975	1976-1977
Staph.aureus	38.5	56.9	59.2	57.9	53.8
Kleb.pneumoniae	58.8	60.0	68.4	69.2	43.6
Entero.cloacae	27.0	23.8	36.7	17.3	10.9
E. coli	40.9	53.8	33.7	24.8	23.8
Proteus mirabilis	19.0	10.8	21.4	7.5	17.6
Ps.aeruginosa	38.5	36.2	63.3	65.4	52.9

#### SEPTICEMIA AND BACTEREMIA IN BURNED PATIENTS

The most significant bacteriologic data acquired from observations on burn patients is the flora recovered in blood culture. Although the opportunistic nature of this secondary invasion is generally recognized, the situation with regard to specific patients is one in which knowledge of septicemic patterns may aid in initiating prompt therapy based on most probable identity of invading organism.

In 1976-1977, 355 patients contributed blood cultures (Table 6). Two hundred-five (205) of these patients had at least one positive blood culture. Thus, 57.7% of all patients with blood cultures drawn exhibited bacteremia. Over the past 3 years, the proportion of patients cultured from whom positives were obtained has remained surprisingly constant - from 54% to 57.7% of patients cultured. This figure suggests that, at least with current burn care, no steps that are being taken lead to diminishing the frequency of bacteremia. Earlier intervals had a lower ratio of positive cultures, for example, in 1971, 35.2%. More species were recognized in 1976-1977 than had previously been recorded. This increase may be in part due to more

Table 6. Blood Culture Isolates from 355 Burn Patients, 1976-1977: Relation of Bacterial Species to Mortality

Species	No. Patients Positive	No. Isolates	% of all Cultured Patients Positive	No. Patients Expired	% of Patients with Positive Cultures Who Expired
<u>Staph. aureus</u>	92	260	25.9	25	27.1
<u>Staph. epidermidis</u>	60	91	16.9	17	28.3
<u>Alpha-hemol. Strep.</u>	4	4	1.1	0	0
<u>Non-hemol. Strep.</u>	6	8	2.3	4	66.0
<u>Strep. Cp. D, entero-coccus</u>	9	21	2.5	3	33.0
<u>Strep. Cp. D</u>	9	21	2.5	3	33.0
<u>Strep. pneumoniae</u>	2	3	0.6	1	50.0
<u>Bacillus sp.</u>	7	7	2.0	1	14.3
<u>Corynebacterium sp.</u>	3	3	0.9	0	0
<u>Micrococcus sp.</u>	8	12	2.3	1	12.5
<u>Ps. aeruginosa</u>	72	182	20.3	35	48.6
<u>Pseudomonas sp.</u>	9	14	2.5	5	55.6
<u>Kleb. pneumoniae</u>	81	184	22.9	31	38.2
<u>Entero. cloacae</u>					
<u>Entero. cloacae</u>	27	43	7.6	11	40.7
<u>Enterobacter sp.</u>	4	4	1.2	2	50.0
<u>E. coli</u>	26	34	7.3	10	38.5
<u>Serratia marcescens</u>	7	12	2.0	4	57.1
<u>liquefaciens</u>	2	3	0.6	0	0
<u>rubidae</u>	1	2	0.3	1	100
<u>Proteus mirabilis</u>	16	29	4.5	3	18.8
<u>morganii</u>	2	4	0.6	1	50.0
<u>Citro. freundii</u>	7	12	2.0	6	85.7
<u>diversus</u>	2	2	0.6	1	50.0
<u>Candida sp.</u>	13	42	3.7	8	61.5

Underlined species represent numerically important organisms.

detailed study of each culture and greater refinement of taxonomic technic. Twenty-four species or genera were recognized, but only 6 of these were numerically important. Table 6 summarizes blood culture results. Staph. aureus, Staph. epidermidis, Ps. aeruginosa, Kleb. pneumoniae, Entero. cloacae and E. coli were each recovered from more than 20 patients. Although Staph. epidermidis is regarded as non-significant clinically, deaths with this species present in blood were at the same rate as was observed with Staph. aureus bacteremia. The clinically significant species were those with a high percentage of all cultured patients positive. Thus, Ps. aeruginosa and Kleb. pneumoniae were, with Staph. aureus, the most important species in septicemia. In previous years, the proportion of patients dying with bacteremia due to these two gram-negative species was much higher than was the case in this series. Fewer than 50% of patients with Ps. aeruginosa bacteremia expired; in earlier years the rate was 80% or higher. One explanation for this difference may be the increased emphasis on blood cultures on patients with no overt signs of sepsis. With more one-time positive cultures, survival rate may increase because the patients are not all exhibiting well-established burn wound sepsis.

The bacteremias listed thus far are in most instances in patients who have more than one species recovered from their blood during their clinical course. With patients in whom only one species is recovered, a truer picture of the relationship of species to lethality emerges. Table 7 shows the results with 10 species, involving 70 patients in whom only one species was recovered. Only three species, Staph. aureus, Kleb. pneumoniae, and Ps. aeruginosa were found in significant numbers and at the same time were associated with mortality. The rates were lower than were noted in similar patients in earlier years, when staphylococci were associated with 25 to 40% mortality and gram-negative single strain bacteremias led to 80% mortality. In this period, 34.1% of all patients with positive blood cultures harbored only one species. The impression that gram-positive cocci in the blood may be relatively innocuous is borne out by this set of observations.

In 66% of patients with bacteremia, more than one species was recovered during the patients' course. This mix was very heterogeneous, as were the combinations of species recovered. In the 1976-1977 interval, blood cultures with more than one strain per patient exhibited the combinations shown in Table 8. The extreme heterogeneity observed in these patients makes it impossible to ascribe any typical pattern or predictable sequence of events to the septicemic process. In terms of sequence, the impression prevails that staphylococcal sepsis often precedes gram-negative sepsis, but a survey of several years' blood cultures does not confirm this assumption. The two most common pairings were Staph. and Pseudomonas (7 patients) and Klebsiella and Pseudomonas (10 patients). The diversity of species capable of invasion and sepsis continues to militate against one-species immunization as a therapeutic measure in burns. As has been observed earlier, the staphylococci are ubiquitous. Possibly they should receive more attention as a species that may pave the way for gram-negative infection in burn patients.

Table 7. Bacteremia With Only One Species of Bacteria Recovered, 1976-1977

Species	No. Patients With One Species Recovered	Ave. No. of Positive Blood Cultures per Patient	Deaths	% Mortality
<i>Staph. aureus</i>	21	2.5	3	14.2
<i>Staph. epidermidis</i>	15	2.0	0	0
<i>Kleb. pneumoniae</i>	16	2.7	6	37.5
<i>E. coli</i>	2	1.0	0	0
<i>Pseudomonas</i> sp.	9	2.6	2	22.2
<i>Strep. non-hemol.</i>	1	1	0	0
<i>Bacillus</i> sp.	1	1	0	0
<i>Citro. freundii</i>	2	2	2	100
<i>Micrococcus</i> sp.	1	2	0	0
<i>Candida</i> sp.	1	1	0	0
Total patients	70			



Table 8. Blood Culture Isolates in Patients with More Than One Species Recovered - 1976-1977

<u>Species</u>	<u>No. of Patients</u>
Staph. aureus, Candida sp.	1
Staph. aureus, Entero. cloacae	1
Staph. aureus, Enterococcus Gp. D	1
Staph. aureus, Kleb. pneumoniae	2
Staph. aureus, non-hemol. Strep.	1
Staph. aureus, Ps. aeruginosa	7
Staph. aureus, Serratia marcescens	1
Staph. epidermidis, Enterococcus, Group D	1
Staph. epidermidis, Ps. aeruginosa	3
Kleb. pneumoniae, Ps. aeruginosa	10
Kleb. pneumoniae, E. coli	4
Kleb. pneumoniae, non-hemol. Strep not D	1
Kleb. pneumoniae, alpha-hemol Strep not D	1
Kleb. pneumoniae, Proteus mirabilis	4
Kleb. pneumoniae, Serratia marcescens	1
Ps. aeruginosa, Entero. cloacae	2
Ps. aeruginosa, Candida sp.	1
Ps. aeruginosa, Serratia marcescens	1
E. coli, Bacillus sp.	1
E. coli, Enterococcus Group D	2
E. coli, Proteus mirabilis	3
Entero. cloacae, Enterococcus Group D	1
Entero. cloacae, Cirto. diversus	1
Kleb. pneumoniae, Prot. mirabilis, Ps. aeruginosa, Serratia	1
No. Patients with 2 spp. recovered:	66
No. Patients with 3 spp. recovered:	0
No. Patients with 4 spp. recovered:	1
No. Patients with Ps. aeruginosa:	29
No. Patients with Kleb. pneumoniae:	25
No. Patients with Staph. aureus:	14
No. Patients with E. coli:	10
No. Patients with Prot. mirabilis:	8
No. Patients with Entero. cloacae:	7

## BIOPSIES AND BURN WOUNDS

Biopsy has become a widely accepted tool for diagnosis of infection in burn wounds, as well as for assessment of the progress of wound healing. Table 9 presents the bacteriologic data from 290 biopsies collected from 113 patients during 1976-1977. There were 371 patients on whom at least one culture was taken; thus biopsies were obtained from 30.4% of patients on whom cultures were taken. Table 9 summarizes this information and notes the relationship between species and mortality for the predominant species. Staph. aureus, Ps. aeruginosa and Kleb. pneumoniae were the numerically important species. Twenty-two species were differentiated, which is a marked increase in the variety of organisms recovered over those recorded in recent years. This difference is only in part due to more detailed speciation in the diagnostic laboratory. Previously unreported gram-negative species included Enterobacter agglomerans, Acinetobacter sp. and Citrobacter freundii. The association of species with mortality is suggested by comparison of number of patients who died with species from biopsy. Kleb. pneumoniae was associated with a mortality rate of 79.4%. Ps. aeruginosa with 54.7% of patients with positive biopsies dying has consistently reflected a lower mortality than is associated with Klebsiella. This heightened incidence and death rate with Klebsiella tissue infections has been noted for the past 2 years. No other major pathogen has emerged recently in this compilation. The behavior of Kleb. pneumoniae in this burn population supports the idea that it is a relatively stable part of the flora, spreading with ease and resistant to all efforts to eradicate it.

## CATHETER TIP CULTURES

Since intravascular infection is always a threat in patients in whom prolonged vascular catheterization is essential, the flora recovered from I.V. catheter tips has been assessed, with the primary purpose of detecting any disproportionate numbers of a particular species or strain that exhibits selective ability to colonize this hazardous site. Table 10 summarizes the findings in this series. The distribution of the major species: Staph. aureus (34.6%) Ps. aeruginosa (26.9%) and Kleb. pneumoniae (30%) parallels that observed in several other special sites and foci that have been studied. Sepsis and wound colonization bacteriology resemble this distribution closely. It may be concluded that the I.V. catheter flora reflects the overall burn wound flora. It was not skewed in any sense which would permit the assumption that a special group of organisms was selectively colonizing intravenous catheters.

The current bacteriologic profile of burn infection in the Institute of Surgical Research is based on 21 months of culture data. The epidemiologic pattern of infection has been less clear than it was in several previous years. Staph. aureus remains a numerically predominant species, in wounds, lung, and blood stream, but the presence of this species did not of necessity connote severe infection or the threat of invasive infection. The most lethal species in terms of invasive infection and the inciting of sepsis was Kleb. pneumoniae. Since 1975, Enterocloacae has receded to a relatively minor part of the bacteriologic picture, but Ps. aeruginosa remained a conspicuous

Table 9. Bacterial Flora of Biopsies of Burn Wounds of 113 Patients - 1 January 1976 - 30 September 1977

Species	No. of Patients Positive	% of Patients Positive	No. of Patients with Positive Cultures Who Expired	% of Patients Who Expired
Staph. coagulase pos.	46	40.7	20	43.5
Staph. coagulase neg.	16	14.2	7	43.8
Alpha-hemol. Strep. not Gp. D	3	2.7	0	0.0
Non-hemol. Strep. not Gp. D	5	4.4	4	80.0
Beta-hemol. Strep. not Gp. A, B, D	1	0.9	0	0.0
Group D Strep. not Enterococci	1	0.9	0	0.0
Group D, Enterococci	2	1.8	1	50.0
Bacillus sp.	16	14.2	6	37.5
Ps. aeruginosa	53	46.9	29	54.7
Pseudomonas sp.	14	12.4	5	35.7
Kleb. pneumoniae	44	38.9	17	79.4
Escherichia coli	8	7.1	3	37.5
Enterocloacae	10	8.8	7	70.0
Enteroc. agglomerans	5	4.4	2	40.0
Enteroc. aerogenes	2	0.9	1	50.0
Proteus mirabilis	9	9.7	4	44.4
Candida sp.	9	9.7	4	44.4
Micrococcus sp.	1	0.9	0	0.0
Acinetobacter calcoaceticus	1	0.9	0	0.0
Serratia marcescens	4	3.5	4	100.0
Citrobacter freundii	3	2.7	2	66.6

No. of specimens: 290

No. of samples per patient (average): 2.6

Table 10. Bacterial Flora of I.V. Catheter Tips  
From 130 Burn Patients, 1976-1977

Species	No. Patients Positive	% of Total Patients Positive
Staph. aureus	45	34.6
Staph. epidermidis	14	10.8
Non-hemol. Strep	8	6.2
Enterococcus Group D	1	0.8
Micrococcus sp	2	1.5
Bacillus sp.	1	0.8
Ps. aeruginosa	35	26.9
Pseudomonas sp	15	11.5
Kleb. pneumoniae	39	30.0
E. coli	6	4.6
Serratia sp	1	0.8
Entero. cloacae	7	5.4
Entero. agglomerans	5	3.8
Citrobacter freundii	2	1.5
Proteus mirabilis	3	2.3
Candida sp	13	10.0

part of the ambient flora, although unequivocal *Pseudomonas* burn wound sepsis was not common. Two species that assumed greater prominence in 1976-1977 were *Proteus mirabilis* and *E. coli*. Neither was as yet present in numbers suggesting epidemic spreads but these species were certainly more in evidence than was formerly the case.

#### PUBLICATIONS

None

#### PRESENTATIONS

Lindberg RB: Burn wound infection and its control. Am Soc. Microbiol., Texas Branch, Galveston, Tx. October 20-23, 1977.



ANNUAL PROGRESS REPORT

PROJECT NO. 3S762774A820-00, MILITARY BURN TECHNOLOGY

REPORT TITLE: STUDIES OF INFECTION AND MICROBIOLOGIC SURVEILLANCE  
OF TROOPS WITH THERMAL INJURY -- THE ROLE OF FUNGI  
IN BURN WOUND INFECTION: OBSERVATIONS ON BIOPSY  
AND AUTOPSY TISSUE FROM SERIOUSLY BURNED SOLDIERS

US ARMY INSTITUTE OF SURGICAL RESEARCH  
BROOKE ARMY MEDICAL CENTER  
FORT SAM HOUSTON, TEXAS 78234

1 October 1976 - 30 September 1977

Investigators:

Robert B. Lindberg, PhD  
Jack R. Henderson, PhD  
Albert T. McManus, Jr, Captain, MSC  
William S. Hardy, Sp5

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## ABSTRACT

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Autopsy and biopsy tissues including burn wound, liver, spleen and lung were cultured routinely for fungi. Fungal colonization was episodic; between episodes no fungi normally appeared, except for *Candida* sp, which were ubiquitous. In biopsy tissue, eight genera of fungi, plus *Candida*, were recovered; 15% of all biopsy samples yielded either yeasts or fungi. Aspergillus and Fusarium were most common. In autopsies, 12 genera of fungi were recovered from wound and viscera. Again, Aspergillus predominated. *Mucor* sp. was recovered from both biopsy and autopsy, and *Rhizopus* sp from autopsy. These species are the primary offenders in fulminating phycomycotic infection in burns, but this syndrome was not observed during the period of observation.

Fungi  
Mucor  
Rhizopus  
Burns  
Phycomycosis  
Humans

STUDIES OF INFECTION AND MICROBIOLOGIC SURVEILLANCE  
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Fungal infection in burn wounds has never been adequately explained. Severe infections are episodic; typically a long period with no observed clinical infections may be followed by an outbreak in which lethal mycotic invasion (caused by *Phycomycetes* in the experience of the Institute of Surgical Research) and a concomittant sharp rise in colonization with saprophytic species occur. This pattern can then abruptly regress. When it occurs, fungal invasion of burn wounds can be rapidly life-threatening, and its control usually involves radical surgical extirpation of the involved tissues.

#### FUNGI IN BIOPSY SPECIMENS

Two hundred ninety biopsies were obtained from 113 patients in 1976-1977. The samples were cultivated on Sabourauds agar and examined over a 6-week period to detect fungi.

Results of this culture routine are shown in Table 1. Nine genera, including *Candida*, were recognized. This rate of recovery was one of the lowest since fungal cultures began on burn patients in this Institute. The progressive drop in fungal colonization on burn wounds is more clearly shown by comparing preceding years (Table 2). It was evident that the number of strains recovered dropped in 1975, and has remained low compared to the recovery rate obtained in 1972. It has been conjectured that fungal growth is less with silver sulfadiazine topical therapy than with sulfamylon cream, but there were years of lower incidence before silver sulfadiazine was introduced.

Table 1. Fungi Recovered from Biopsies, 1976-1977

Genus	No. of Patients Positive	No. of Strains Recovered
<i>Aspergillus</i>	4	5
<i>Trichophyton</i>	1	1
<i>Fusarium</i>	4	4
<i>Cephalosporium</i>	3	4
<i>Sepedonium</i>	2	3
<i>Penicillium</i>	1	1
<i>Alternaria</i>	2	3
<i>Mucor</i>	1	1
<i>Candida</i> sp	14	22

Table 2. Comparison of Annual Recovery of Fungi, 1972-1977

Genus	1972	No. Strains Recovered			1976-1977
		1973	1974	1975	
<i>Aspergillus</i>	11	17	5	2	5
<i>Cephalosporium</i>	15	5	5	1	4
<i>Fusarium</i>	33	23	17	2	4
<i>Sepedonium</i>	0	1	0	0	3
<i>Penicillium</i>	1	1	3	0	1
<i>Alternaria</i>	7	2	3	1	3
<i>Trichophyton</i>	0	0	0	0	1
<i>Mucor</i>	2	2	0	0	1
<i>Curvularium</i>	3	2	3	0	0
<i>Scopulariopsis</i>	11	0	0	0	0
<i>Diplosporium</i>	1	0	0	0	0
<i>Helminthosporium</i>	0	9	2	0	0
<i>Rhizopus</i>	3	2	0	0	0
<i>Geotrichum</i>	1	0	4	0	0
<i>Candida</i> sp	46	141	144	15	22
No. Patients Cultured:	201	106	135	63	113

## FUNGI RECOVERED FROM TISSUES OF BURN PATIENTS AT AUTOPSY

The recovery rate of fungi from tissues at autopsy has been higher than that obtained from biopsies. It has been suggested that the burn wound, accessible to the environment, would be more heavily colonized than the viscera, i.e. liver, spleen and lung. The result of culture of 97 autopsies in 1976 and 1977 is shown in Table 3. There were 10 genera and 43 strains recovered from burn wounds, and 8 genera with 62 strains recovered from viscera. There was no essential difference in the colonization of the two site categories. The wounds harbored two more genera than viscera, but more strains were recovered from viscera. In contrast to the period 1971-1974, *Fusarium* spp were not numerous in this interval. The most common genus was *Aspergillus*; no other saprophyte genera were conspicuous. As in preceding surveys, the Phycomycete group, including *Mucor* and *Rhizopus*, was present but in small numbers. The frequency with which fungi were encountered was comparable to that seen in two preceding years. It may well be that the observed incidence represents a minimal rate, which may be expected to persist.

Continual monitoring of wounds and autopsies for fungi is mandatory. There is no apparent reason for the gradual decrease in incidence of fungi in burn patients at the Institute of Surgical Research, nor is there any reason to assume the incidence could not revert abruptly. When Phycomycosis



Table 3. Genera of Fungi Recovered from Viscera  
(Lung, Liver, Spleen) and Burn Wound at Autopsy, 1976-1977

Genus	Wounds		Viscera	
	Patients Positive	No. Strains	Patients Positive	No. Strains
Aspergillus	15	23	21	41
Sepedonium	2	3	1	1
Fusarium	2	4	2	2
Penicillium	1	1	5	6
Trichophyton	0		1	1
Alternaria	2	2	3	3
Mucor	2	4	3	3
Geotrichum	2	3	0	
Cephalosporium	0		5	6
Diplosporium	1	1	0	
Rhizopus	1	1	0	
Helminthosporium	1	1	0	

has appeared in patients at this Institute, it has always been accompanied by a marked increase in incidence of saprophytic genera in burn wounds and in viscera of burn fatalities. Monitoring as it is carried out here is a plausible way to anticipate a recurrence of mycotic infection in burns. The consequences of invasive mycoses can be so grave, that any warning that such might impend is of potential usefulness.

#### PRESENTATIONS/PUBLICATIONS

None

ANNUAL PROGRESS REPORT

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Control of bacterial infection in burn patients is still a major problem, and the recurrent prospect of emergence of resistant forms makes new topical formulations highly desirable. This study explored the area of new metal-sulfonamide compounds. Zinc, copper, chromium and cerium were combined with sulfadiazine and sulfamethoxazole in a series of defined compounds and tested in a cream base on burned rats seeded with virulent Pseudomonas aeruginosa. Three challenge strains were used. Survival ranged from the 95% range for Ag and Cr sulfadiazine to 25% for Ag and Cu sulfamylon. Several compounds of experimental therapeutic potential exceeding that of silver sulfadiazine were developed. Blood levels of sulfadiazine, as a reflection of rate of dissociation and absorption of components, were lower for the experimental compounds than they were with silver sulfadiazine. Potential topical therapeutic agents may reside in this group of experimental compounds.

Pseudomonas  
Topical therapy  
Burns  
Silver  
Heavy metal cations  
Humans

STUDIES OF INFECTION AND MICROBIOLOGIC SURVEILLANCE OF  
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MILITARY PATIENTS: THE SEARCH FOR NEW FORMULATIONS

Suppression or control of burn wound flora is essential if patients with extensive burns are to survive. Without effective suppression of the bacterial flora, burn wounds become progressively more heavily infected, and ultimately tissue invasion, sepsis and death ensue. The armamentarium of topical agents currently in use to control burn wound infection include Sulfamylon, silver-sulfadiazine, silver nitrate and Betadine as major agents. Emerging microbial resistance to some agents, and undesirable side effects with others, suggest that further exploration of this area is merited. There is a high incidence of deaths due to sepsis, with massive proliferation of bacteria in extensive burn wounds, with each of the major topical agents. This situation further supports the need for further improvement in topical formulations for treating burns.

The seeded burned rat model for producing experimental *Pseudomonas* burn wound sepsis has been used for many years in the Institute of Surgical Research. No other experimental infection model produces as convincing a simulation of the disease in human burn victims. This model has been used in the experiments described herein seeking better understanding of the mode of action of topical therapeutic agents and improved formulas for the treatment of burns.

The successful development of silver-sulfadiazine as a topical agent prompted further study of metal sulfonamide and metal-methylated sulfonamide compounds. Zinc-sulfadiazine has been reported as showing desirable properties as a topical therapeutic agent, and was examined in detail in comparison with silver sulfadiazine in treatment of experimental *Pseudomonas* sepsis. The antibacterial action of heavy metals was studied extensively in the 1920s and 1930s. Cations were arranged in order of increasing toxicity for *Escherichia coli* (1). This offered a basis for selecting other ions that would merit testing. The metals of interest in this study have been, in order of increasing toxicity, zinc, copper and cerium. Chromium, on the basis of its action as chromate, was also included.

#### TECHNIC

The metals as soluble salts were each mixed with a solution of the various sulfonamides. Precipitation was rapid and relatively complete; the metal-sulfonamides were only slightly soluble. On the basis of combining ratios and of physical characteristics, a strong presumption exists that the preparations were indeed compounds of constant composition. The preparations were dried, dispersed as a powder or with a finely granular consistency,

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1. Winslow C. -EA, Hotchkiss M: Action of heavy metals on bacteria. Proc. Soc. Expt. Biol. Med. 19: 314, 1922.



and were made up in concentrations ranging from 1% to 10% in water-dispersible cream base. The test model was the standard ISR burned rat model: a 20% full-thickness scald on the dorsum of a 200 gram rat, anesthetized and shorn with electric clippers over the burn area. The rats to be infected were seeded with in 90 minutes postburn with  $10^8$  cells of a broth culture of the challenge strains.

Test organisms were challenge strains, each with a long pedigree of proven virulence in this preparation. They included three major test strains: 12-4-4-59, 8-28-3-63 and VA-134. These strains have been exhaustively documented on the rat model which was used. Over a long period, 12-4-4 has been approximately 90% virulent.; type 8-28-3 is 94% virulent; and VA-134 is 100% virulent. Per cent of virulence signifies the proportion of deaths which were incurred by rats seeded with Pseudomonas aeruginosa but not treated. Several other virulent test strains were used with some of the compounds, and it is planned to test all compounds with this complete test set.

Compounds tested included: (a) zinc sulfadiazine; (b) zinc sulfamethoxazole; (c) zinc Sulfamylon; (d) zinc sulfamethazine; (e) copper sulfadiazine; (f) copper Sulfamylon; (g) cerium sulfadiazine and (h) chromium sulfadiazine.

The objective was to determine the therapeutic potential of each compound, its toxicity on the burned rat, its effect on the bacterial content of the rat wound, and blood levels of drug. This last value offers a clue as to the readiness with which the compound dissociates. Multiple tests were desirable to confirm the therapeutic action; as has been observed with tests of other topical compounds, therapeutic response can occasionally vary markedly with individual sets of animals. The study is not yet completed, but indications of therapeutic potential are at hand.

Zinc sulfadiazine was the first compound tested and its behavior in various concentrations is summarized in Table 1. The results in this and all other tests were expressed in terms of a fraction, with surviving animals as the numerator and total test animals as the denominator. The dose-response relationship was evident; while the survival with strain 12-4-4 was complete using a 1% zinc sulfadiazine cream, the more virulent 8-28-3 required 2% to 3% for complete survival. The highly virulent VA-134 killed 55% of rats at the 1% concentration, and only 10% zinc sulfadiazine permitted complete survival of rats seeded with this strain. The behavior of zinc sulfadiazine in 3% concentration essentially paralleled the survival achieved with 1% silver sulfadiazine. With four additional challenge strains, of which two were 100% lethal, only 3% zinc sulfadiazine was tested in comparison with silver sulfadiazine. At this level, survival rates were comparable, but lower concentrations of zinc sulfadiazine are also scheduled to be tested. This zinc containing compound was not toxic for unseeded burned rats.

Copper sulfadiazine was tested in 2½% and 5% concentrations (Table 2) Preliminary trial suggested a 1% concentration might be too low in activity to merit testing. The 2½% level was as effective as the silver sulfadiazine; 5% copper Sulfamylon was slightly more effective than the 2½% concentration. The preparation had no discernible effect on burned, unseeded rats when applied

Table 1. Zinc Sulfadiazine in Control of Experimental *Pseudomonas*  
Burn Wound Sepsis in Burned, Seeded Rats

Challenge Strain	% of Zinc Sulfadiazine and Survival Rate (Survival/Total Tested)					Silver Sulfadiazine	Control (Inoculated, not treated)
% Concentration	1	2	3	6	10	1	
12-4-4 % Survived No. Trials	12/12 100 2	9/10 90 2	13/14 92.8 3	10/10 100 2		39/46 84.7 8	1/37 2.7 8
8-28-3 % Survived No. Trials	18/21 85.7 4	10/10 100 2	15/16 93.7 3	15/15 100 3		37/41 90.2 8	1/42 2.3 8
Va-134 % Survived No. Trials	5/11 45.4 2		12/16 75 2		15/15 100 3	19/29 65.5 6	0/34 0 6
3-23-11 % Survived			5/5 100			5/5 100	0/5 0
6-14-3 % Survived			5/5 100			10/11 90.9	2/4 50
7-14-20 % Survived			3/5 60			8/11 72.7	2/5 40
3-13-36 (A71) % Survived			10/11 90.9		15/15 100	18/20 90	0/18 0

over a 10-day period. The therapeutic potential shown merits further study.

Table 2. Copper Sulfadiazine in Control of Experimental Pseudomonas Burn Wound Sepsis in Burned, Seeded Rats

Challenge Strain	Concentration of Cu Sulfadiazine and Survival Rate		Silver-Sulfadiazine 1%	Untreated Control
	2½%	5%		
12-4-4	5/5	5/5	9/10	1/12
8-28-3	8/10	17/17	14/16	0/16
VA-134	5/5	8/10	8/16	0/15

Cerium nitrate has been described as adding therapeutic effectiveness to silver sulfadiazine when it is added in small quantities. Since the lanthanum group of metals have been considered as potential antibacterial agents, a trial of cerium sulfadiazine was deemed warranted. Table 3 summarizes the results of treatment with 1% and 5% cerium sulfadiazine. The 1% concentration was highly effective in control of experimental burn wound sepsis; the increased survival observed when the 5% concentration was used is considered marginal and may, on further study, disappear. The variation in responses between challenge strains was more evident with cerium sulfadiazine than it was with other metal sulfadiazine compounds.

Table 3. Cerium Sulfadiazine in Control of Experimental Pseudomonas Burn Wound Sepsis in Burned Seeded Rats

Challenge Strain	Concentration of Cerium-Sulfadiazine & Survival Rate		Silver-Sulfadiazine 1%	Untreated Control
	1%	5%		
12-4-4	5/5	4/5	15/15	1/10
8-23-3	5/5	5/5	13/13	0/12
VA-134	1/5	3/5	8/16	0/16
3-13-36(A-71)	3/5	5/10	2/11	0/11

The fourth sulfadiazine metal compound to be evaluated was chromium sulfadiazine (Table 4). The effect of 1% of this compound was as great as that achieved with the 5% strength. One per cent chromium sulfadiazine was

as effective in preventing sepsis as was 1% silver sulfadiazine.

The behavior of these four metal sulfonamide compounds suggested a general pattern as it applies to control of *Pseudomonas* burn wound sepsis. Each of them closely resembled silver sulfadiazine, yet the metal ions vary widely in bacteriostatic activity. Neither copper nor cerium is nearly as active as silver in antibacterial activity. It is possible that the metal sulfonamide linkage is responsible for a synergistic effect that is independent of the identity of the metal per se.

Table 4. Chromium Sulfadiazine in Control of Experimental *Pseudomonas* Burn Wound Sepsis in Burned, Seeded Rats

Challenge Strain	Concentration Used & Survival Rate of Chromium Sulfadiazine		Silver-Sulfadiazine 1%	Untreated Control
	1%	5%		
12-4-4	10/11	10/10	9/9	0/12
8-28-3	10/10	10/10	14/15	0/14
VA-134	2/5	3/5	9/14	0/15

Sulfamethoxazole was shown, in earlier studies, to be remarkably effective as a topical agent in suppressing *Pseudomonas* burn wound sepsis. The zinc sulfamethoxazole was, in consequence, perceived as a promising formulation. The results of the first trials of this compound confirm this supposition (Table 5). The protection afforded by 1% zinc sulfamethoxazole was high enough, especially with the more virulent challenge strains, to justify further study of this compound. Even with strain VA-134, the most virulent challenge strain, 62% of the animals survived. This is slightly higher than a typical survival with silver sulfadiazine.

Table 5. Zinc Sulfamethoxazole in Control of Experimental *Pseudomonas* Burn Wound Sepsis in Burned, Seeded Rats

Challenge Strain	Concentration of Zn-Sulfamethoxazole and Survival Rate		Untreated Control
	1%	5%	
12-4-4	10/10	10/10	0/9
8-28-3	9/10	5/5	1/10
VA-134	10/16	9/11	0/10



Future experiments will further assess the behavior of sulfamethoxazole itself. Compounds other than sulfamethoxazole are not comparable on any basis which relates structure to function.

In addition to assessing the behavior of metal sulfadiazine compounds, it appeared plausible that metal Sulfamylon compounds might show some therapeutic advantage. Two of them, zinc Sulfamylon and copper Sulfamylon were tested. The compounds were compared with 5% Sulfamylon.

Zinc Sulfamylon, even at 5% concentration, had less therapeutic effect than Sulfamylon itself (Table 6). With the more virulent strains, the discrepancy was even greater. The control Sulfamylon was only a 5% concentration, and applied once daily; still it permitted survival for 40% of the VA-134 group. The zinc Sulfamylon had no survivors from infection caused by that strain.

Table 6. Zinc Sulfamylon in Control of Experimental Pseudomonas Burn Wound Sepsis in Burned Rats

Challenge Strain	Concentration of Zinc Sulfamylon and Survival Rate		Sulfamylon 5%	Untreated Control
	1%	5%		
12-4-4	1/5	2/5	5/5	1/5
8-23-3	0/5	0/5	4/5	0/5
VA-134	0/10	0/10	2/5	0/5

The results of the testing of copper Sulfamylon are summarized in Table 7. This was even less effective than zinc Sulfamylon. The only survival came with strain 8-28-3. It was not, however, sufficient to suggest further investigation of this compound.

Table 7. Copper Sulfamylon in Control of Experimental Pseudomonas Burn Wound Sepsis in Burned Rats

Challenge Strain	Concentration of Cu Sulfamylon and Survival Rate		Sulfamylon 5%	Untreated Control
	1%	5%		
12-4-4	0/5	0/5	5/5	0/5
8-23-3	1/10	1/5	5/5	0/5
VA-134	0/5	0/5	2/5	0/5

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ANNUAL RESEARCH PROGRESS REPORT, 1 OCTOBER 1976-30 SEPTEMBER 19--ETC(U)  
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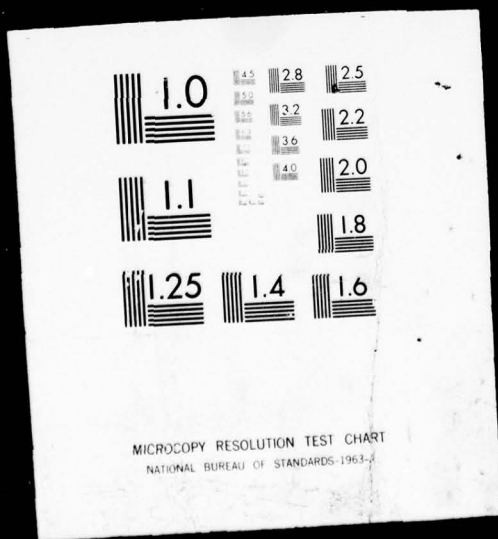
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A fourth category of sulfonamides was investigated with the formulation of zinc sulfamethazine. Table 8 summarizes the results of testing this compound in 1% and 5% concentrations. It was entirely without virtue in controlling sepsis. This category of sulfonamides do not justify further study.

Table 8. Zinc Sulfamethazine in Control of Experimental Pseudomonas Burn Wound Sepsis in Burned Rats

Challenge Strain	Concentration of Zinc Sulfamethazine and Survival Rate		Untreated Control
	1%	5%	
12-4-4	1/5	2/5	0/5
8-28-3	0/5	0/5	0/5
VA-134	0/10	0/10	0/9

Blood levels were determined in rats being treated with zinc sulfadiazine, zinc sulfamethoxazole, copper sulfadiazine and chromium sulfadiazine. The level reflects the dissociation of the metal sulfonamide compounds, which were extremely insoluble. The levels of zinc sulfadiazine treated rats were determined in parallel with samples from rats being treated with silver sulfadiazine. A representative set of values is shown in Table 9.

Table 9. Blood Levels of Sulfadiazine from Burned, Seeded Rats Treated with Zinc Sulfadiazine and Silver Sulfadiazine

Compound	Day Post-seeding and Sulfadiazine Level (mg%): Individual Rats		
	3 Days	6 Days	9 Days
Zinc Sulfadiazine 3%	0.69	3.8	3.8
	0.93	3.0	4.5
	0.62	4.8	4.5
Silver Sulfadiazine 1%	1.97	7.3	7.04
	1.52	6.7	7.26
	0.41	5.5	5.18

The blood levels of sulfadiazine in the sulfadiazine-treated rats were considered to be within an acceptable range. Treatment was carried on into the day in which the rats were sacrificed. Later trials, still not completed, gave lower results for both zinc and silver sulfadiazine, but most important



was the fact that the blood levels of sulfadiazine in the zinc sulfadiazine treated animals were significantly lower than those for silver sulfadiazine. It is a valid presumption that since the sulfonamide comes from dissociation of the zinc sulfonamide compound, the available metal would be present in a similar proportion. Although metal ion levels have not yet been done, it is plausible to assume that even less zinc than silver was released and absorbed.

Subsequent blood level experiments have, on three successive trials, given lower values than were obtained on the first trial. The mean level for zinc sulfadiazine at 3 days of application was below 1.0 ug%, and at 6 days the level was from 1.5 to 2.5 ug%. Further tests are planned to clarify this variation.

#### DISCUSSION

The evaluation of new compounds of potential value as topical agents for control of infection in burn wounds is invariably a complex procedure. A valid test system is essential with multiple challenge strains used, since response to therapy has been shown to vary among strains. The optimal dose of therapeutic agent must be derived by trial and error aided by informed presumptions. The studies described show that the initial agent, zinc sulfadiazine, has real prophylactic properties, but somewhat to our surprise, other cations in similar combinations have shown even more in vivo promise. The behavior of copper, cerium and chromium in combination with sulfamethoxazole and further tests of sulfadiazine compounds are strongly indicated. Even if new agents do not perform beyond the level of available formulations, the fact that they are different could be of importance in topical therapy. A succession of potent suppressive agents might well be more effective than a single compound.

#### PRESENTATIONS AND/OR PUBLICATIONS

None

ANNUAL PROGRESS REPORT

PROJECT NO. 3S762774A820-00, MILITARY BURN TECHNOLOGY

REPORT TITLE: STUDIES OF INFECTION AND MICROBIOLOGIC SURVEILLANCE  
OF TROOPS WITH THERMAL INJURY - - BACTERIOPHAGE  
TYPES OF SERRATIA MARCESCENS FROM BURN WOUNDS OF  
MILITARY PERSONNEL

US ARMY INSTITUTE OF SURGICAL RESEARCH  
BROOKE ARMY MEDICAL CENTER  
FORT SAM HOUSTON, TEXAS 78234

1 October 1976 - 30 September 1977

Investigators:

Virginia C. English, MS  
Robert B. Lindberg, PhD  
Basil A. Pruitt, Jr, MD, Colonel, MC  
Arthur D. Mason, Jr, MD

REPORTS CONTROL SYMBOL MEDDH-288(R1)

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## ABSTRACT

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Previous application of a proposed phage typing system for Serratia marcescens revealed technical problems that made propagation of phage strains ineffective. The system was re-examined to determine the nature of the problem and to develop a solution. It has been found that the proliferative stage of phage propagation is, in some phage strains, accompanied by a uniquely rapid emergence of resistant forms, which appear to be cells resistant to lysis due to presence of a specific pro-phage. The technic has been reassessed and revised; it has proven possible to achieve high titers of specific phage by using younger cultures in seeding, thus obtaining far larger quantities of phage before the resistant population appears.

New isolation procedures have been carried out to broaden the spectrum of phages available. Four phages of the earlier set have been retrieved and obtained in high titer. Four new phages are in an advanced stage of characterization, and cross-reaction patterns of identity are now being determined. An improved, reproducible typing set is now in prospect; within 4 to 6 months the system should be restructured to a point at which it can be applied not only to strains of S. marcescens from the Institute of Surgical Research but to strains from other sources.

The usefulness of a workable phage typing set for S. marcescens has been evident in both nosocomial epidemics in the Institute of Surgical Research and in other hospitals in this area and abroad. An ubiquitous opportunistic species such as S. marcescens must be viewed as a continued threat to patients in a burn ward. Thus far, local outbreaks appear to be self-limiting, but there is no basis for optimism that this will continue to be the case.

A stock collection of S. marcescens strains from local isolation has been gathered, and strains from other sources are being collected to determine the breadth of coverage of the developing phage set. The objective of a broadly applicable typing set for S.marcescens appears to be in prospect of achievement.

Burns  
Serratia  
Bacteriophage  
Humans



ANNUAL PROGRESS REPORT

PROJECT NO. 3S762774A820-00, MILITARY BURN TECHNOLOGY

REPORT TITLE: STUDIES OF INFECTION AND MICROBIOLOGIC SURVEILLANCE  
OF TROOPS WITH THERMAL INJURY -- SENSITIVITY TO  
SULFAMYLDON OF PSEUDOMONAS AERUGINOSA RECOVERED  
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Six hundred ninety-eight strains of *Pseudomonas aeruginosa* were tested for sensitivity to Sulfamylon using an agar dilution technic. Strains were highly sensitive overall; the median sensitivity was 0.117% in 1976-1977. This level was lower than the 10-year average of 0.134%. Specific serotype and phage type epidemics had causative strains that tended to be more resistant than the microbial population overall. Other monotype epidemics could exhibit increased sensitivity to the drug. The behavior of serotypes and phage types was, to a considerable degree, parallel.

*Pseudomonas*  
Burns  
Sulfamylon  
Topical therapy  
Humans

STUDIES OF INFECTION AND MICROBIOLOGIC SURVEILLANCE OF  
TROOPS WITH THERMAL INJURY --  
SENSITIVITY TO SULFAMYLON OF *PSEUDOMONAS AERUGINOSA*  
RECOVERED FROM BURNED SOLDIERS

Invasive infection in burn wounds is a frequent complication of thermal injury, and an antibacterial barrier on the burn itself has been recognized as of paramount importance, since control of such infection is a basic requirement for survival of patients with extensive burns. Topical therapy is a major means of effecting such control. In this Institute, Sulfamylon<sup>®</sup> burn cream was used as the initial treatment modality for 10 years following its development. Currently, initial topical treatment employs silver-sulfadiazine, with Sulfamylon introduced later in the course of treatment as required. Five per cent Sulfamylon aqueous solution, applied on gauze soaks, is an important part of the treatment modality aimed at controlling the risk of invasive infection during the stage of eschar separation and the healing of the burn wound to the point where skin grafting becomes possible. It is virtually a truism that all antibacterial agents, when used over a prolonged period, permit the emergence of antibiotic resistant forms, and it was assumed that *Pseudomonas aeruginosa*, the pathogen toward which Sulfamylon was originally directed, would follow this pattern. The burn wound flora was at first monitored for sensitivity of all major infecting species to Sulfamylon. Later, it was concluded that monitoring the behavior of *Ps. aeruginosa* isolates would furnish adequate indication of the ability of Sulfamylon to suppress all burn wound flora. It has, over several years of observation, become apparent that this compound is unique among substances used in topical therapy of burns, in its continued ability to inhibit *Ps. aeruginosa*, despite continuous exposure of burn wound flora to this drug during the past 13 years. From one year to the next, there have been fluctuations in the proportion of strains inhibited at a given concentration, but no genuinely resistant strains have been found. It is possible that multiple sites of action of Sulfamylon exist, so that a mutation at more than one site would be required for resistance to be manifest. Whatever its cause, the fact of long-continued sensitivity remains.

Testing for sensitivity to Sulfamylon was done by an agar plate dilution method. The drug was incorporated into agar plates at dilutions ranging from 0.019% to 2.5%.

SENSITIVITY OF *PSEUDOMONAS AERUGINOSA* TO SULFAMYLON

This report covers a period of 21 months, from 1 January 1977 to 30 September 1977. There were 698 strains of *Ps. aeruginosa*. Sensitivity of this group to Sulfamylon is shown in Table 1. The inhibiting concentrations with Sulfamylon, as with many sulfonamides, were in the grams per 100 ml range. On the basis of extended experience with this drug and of sensitivity levels recorded over the years of testing, it has been concluded that strains inhibited by 0.312% may be designated as sensitive. This level is 1/32 of the concentration of Sulfamylon burn cream, which was originally developed as a 10% concentration in a water-dispersible cream. At the 0.312% level or be-

Table 1. Sensitivity to Sulfamylon for  
Pseudomonas aeruginosa, 1976-1977

No. Strains	Concentration Required for Inhibition in gm/100 ml	% of Total Tested
4	1.25	0.5
118	0.625	16.9
135	0.312	19.3
295	0.156	42.2
95	0.078	13.6
18	0.039	2.5
23	0.019	3.2
10	<0.019	1.4
698 = Total		

low, 82.5% of all strains tested with inhibited in 1976-1977.

Since the point of particular interest in the sensitivity of Ps. aeruginosa to Sulfamylon was the persistence of a constant role of sensitivity despite prolonged exposure to the drug, earlier sensitivity levels were tabulated by annual increments. Table 2 presents this data extending by annual increments back to 1972. The 1976-1977 collection showed a proportion of patients sensitive to increasing levels of drug which was quite comparable to the 5-year average of numbers of strains inhibited at various levels, except that the number inhibited by 0.156% was higher than the average.

The similarities and variations observed in the sensitivity of Pseudomonas to Sulfamylon over a period of 10 years may be more clearly visualized when set down as cumulative sensitivity in per cent of total strains tested (Table 3). In 4 of these 10 years, all strains were inhibited by 0.625% Sulfamylon, and from 83 to 100 per cent were inhibited by 0.312%. Since 1973, the largest proportion requiring 0.625% for inhibition was 2.2%. During that later period, sensitivity has remained relatively constant.

The median sensitivity level, at which 50% of the strains are inhibited, offers a simple numerical value that expresses the average sensitivity for a group of strains. Table 4 shows this information starting, as did the cumulative summary, with 1967. The relative constancy of the sensitivity of Ps. aeruginosa over these years is apparent.

This consistency of sensitivity is most clearly shown when the annual increments are shown graphically. This information for the years 1971 through September 1977 is shown in the figure. The unexplained marked increase in Sulfamylon tolerance in 1972 is the only aberration in an otherwise extremely



Table 2. Inhibiting Concentrations of Sulfamylon for *Pseudomonas aeruginosa*  
1972-1977

Year	No. of Strains	2.5	1.25	Concentration of Sulfamylon in % gm/100 ml						
				0.625	0.312	0.156	0.078	0.039	0.019	< 0.019
1972	463	0	29	212	46	88	31	37	15	5
% of total		0	6.3	45.8	9.9	19.1	6.7	7.9	3.2	1.1
1973	285	0	4	14	85	85	52	32	12	1
% of total		0	1.4	4.9	19.8	29.8	18.3	11.2	4.2	0.4
1974	437	0	5	59	78	97	97	86	11	4
% of total		0	1.1	13.5	18.0	22.2	22.2	19.7	2.5	0.9
1975	637	1	13	113	108	155	68	147	28	4
% of total		0.16	2.0	17.7	16.9	24.3	10.7	23.1	4.5	0.64
1976-1977	698	0	4	118	135	295	95	18	23	10
% of total		0	0.57	16.91	19.37	42.26	13.61	2.58	3.30	1.43
Total 1972-1977	2520	1	555	516	452	720	343	320	89	24
% of total		0.04	2.18	20.48	17.94	28.57	13.61	12.70	3.53	0.95

Table 3. Cumulative Sensitivity to Sulfamylon of Pseudomonas aeruginosa  
1967-1977

Year	No. of Strains	Per Cent Concentration and Percent of Strains Inhibited									
		2.50	1.25	0.625	0.312	0.156	0.078	0.039	0.019	< 0.019	
1967	471	100	100	96.8	87.6	81.7	61.3	46.4	15.6	-	
1968	294	100	100	100	95.1	60.4	45.8	14.1	1.7	-	
1969	385	100	100	100	96.5	50.0	26.9	7.7	0.5	-	
1970	296	100	100	100	100	78.0	49.9	21.9	2.0	-	
1971	280	100	100	100	82.9	68.3	48.3	27.9	4.7	-	
1972	463	100	100	93.7	48.0	38.0	19.0	12.3	4.3	1.1	
1973	285	100	100	98.1	81.3	57.0	33.5	16.1	3.2	0.4	
1974	437	100	100	99.0	85.5	67.5	45.3	23.1	2.4	0.9	
1975	637	100	99.8	97.8	80.1	63.2	38.9	24.2	5.1	0.64	
1976- 1977	698	100	100	99.43	82.52	63.18	20.92	7.31	4.73	1.43	

consistent set of values.

Table 4. Median Value of *Pseudomonas aeruginosa*  
Sensitivity to Sulfamylon: 1967-1977

Year	No. of Strains	Median Inhibitory Level % Concentration
1967	471	0.083
1968	294	0.136
1969	385	0.176
1970	296	0.068
1971	280	0.125
1972	463	0.316
1973	285	0.111
1974	437	0.086
1975	637	0.125
1976-1977	698	0.117
Total: 10 years	4246	0.134

Sensitivity to antimicrobial agents is customarily determined on a sample of a bacterial population. However, it could be of great importance if it could be shown that specific epidemic strains of *Ps. aeruginosa* vary in their response to such antimicrobials as Sulfamylon. A group of 105 strains, serotyped with the proposed international typing system, were collected during a time when two epidemic types were present on the burn ward in overlapping time periods over a 3-month interval. Three types of lesser numerical importance were recognized at the same time. Table 5 shows the sensitivity distribution of these strains. Type 4 included 69 strains from varying sources. The median inhibitory level for all strains in 1976-1977 was 0.117%. The median level of inhibition for the epidemic type 4 strains was 0.373%. During the latter part of the epidemic period, a second episode with type 15 occurred. All strains of this type fell in the 0.312 to 0.625% range of sensitivity. The median value was 0.478%, in contrast to the annual median value of 0.117%. The remaining strains were dispersed over a range consistent with the annual median level of sensitivity.

It was apparent that the two predominant types differed from the whole group of *Ps. aeruginosa* tested in this year. This work is being extended to a larger sample to determine the presence of predominant types which may vary from the median level of sensitivity. The sequence of appearance of a more resistant strains which could, because of this attribute, spread to become dominant on the burn ward, is plausible. Such information could be useful in planning optimal regimens of antimicrobial agents for ongoing prophylaxis in burn patients.

Sensitivity of *Ps.aeruginosa*  
to Sulfamylon:1971-1977

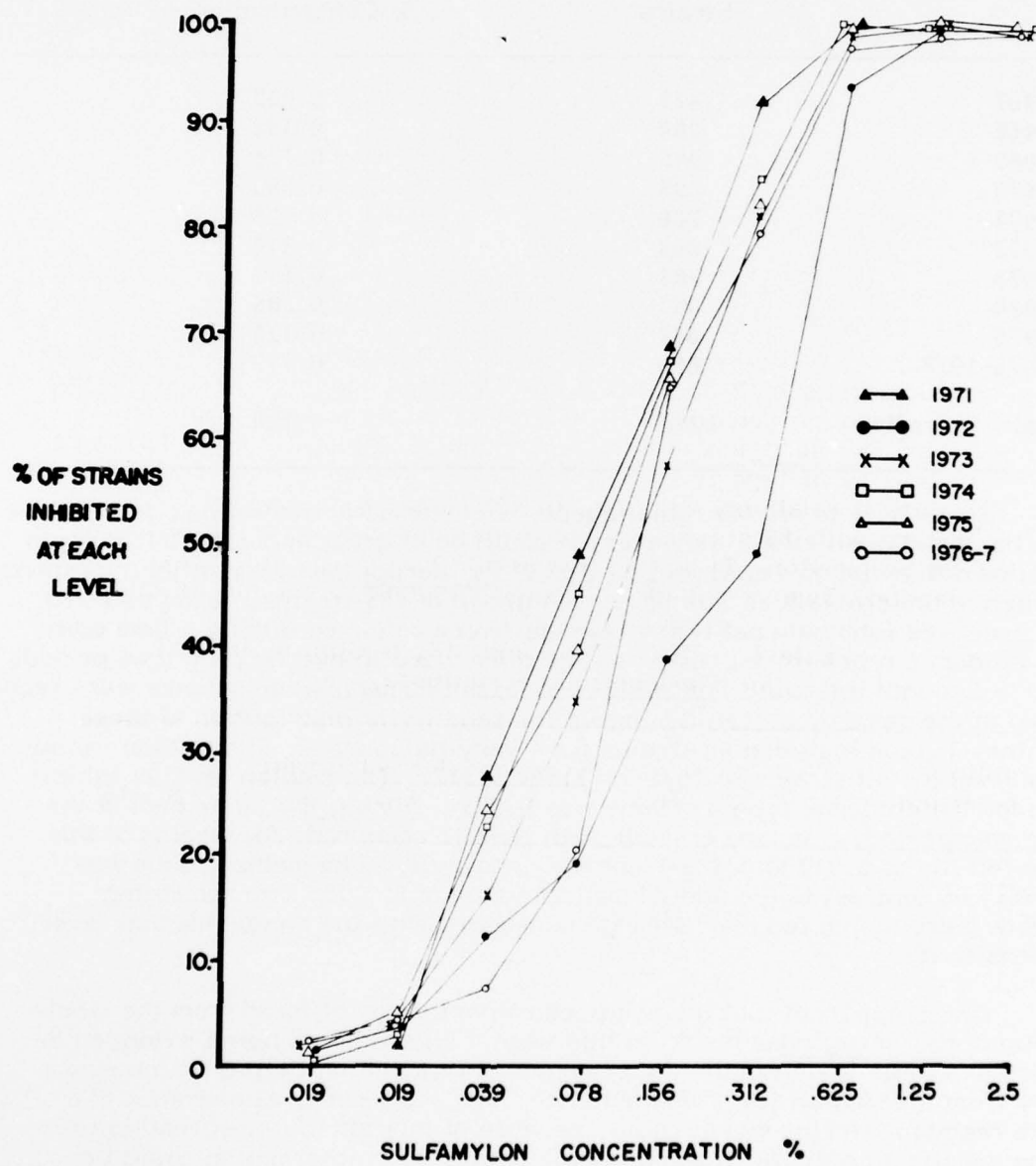




Table 5. Serotype and MIC of Sulfamylon for *Pseudomonas aeruginosa*, 1976-1977

Inhibitory Concentration	4	Serotype and No. of Strains				Total
		8	4, 9, 10	11	15	
1.25						
0.625	21		5		8	34
0.312	36		1	2	7	46
0.156	6	5		1		12
0.078	6	1	3			10
0.039						
0.019						
0.019			3			3
Totals	69	6	12	3	15	

To compare the behavior of a serotyped group with a phage typed group, the identities of *Pseudomonas* strains collected in 1975 were correlated with Sulfamylon sensitivity. Table 6 summarizes the sensitivity of 150 strains of *Ps. aeruginosa* distributed among 3 phage types. Thirty-five of 47 isolates of type H-1 required 0.625% of Sulfamylon for inhibition. This was a relatively resistant group. Type E-2 appeared in epidemic numbers with 83 strains collected; 80 of these were inhibited by only 0.039% Sulfamylon. Type HT-16 was the most resistant strain in this whole collection. Twelve out of 20 strains required 1.25% for inhibition.

Table 6. Phage Type and MIC of Sulfamylon for *Pseudomonas aeruginosa*, 1975

Inhibitory Concentration	H-1	Type and No. of Strains		NT-16
		E-2		
1.25				12
0.625	35			6
0.312	3	1		1
0.156				1
0.078	1	2		
0.039	2	68		
0.019	6	9		
0.019		3		
Totals	47	83		20

Both serotype and phage type classification permit one to delineate groups of epidemic strains of unusual sensitivity to Sulfamylon - either high sensitivity or high resistance. Epidemic episodes are frequently monotype and they can vary widely in sensitivity from the median level for this species over a longer period. The relationship of such variations to virulence, invasiveness and the likelihood of appearance of sepsis are being further investigated. Correlation of typing characteristics and sensitivity data will guide more selective study of this important pathogen.

#### PRESENTATIONS

Lindberg RB: Pseudomonas aeruginosa in the Hospital Environment. Presented at seminar on "Microbiology of Contaminated Surfaces", Am Soc Microbiol. 1977, New Orleans, La.

#### PUBLICATIONS

None

ANNUAL PROGRESS REPORT

PROJECT NO. 3S762774A820-00, MILITARY BURN TECHNOLOGY

REPORT TITLE: STUDIES OF INFECTION AND MICROBIOLOGIC SURVEILLANCE  
OF TROOPS WITH THERMAL INJURY -- DETECTION OF  
ENDOTOXIN IN BURNED SOLDIERS WITH SEPSIS

US ARMY INSTITUTE OF SURGICAL RESEARCH  
BROOKE ARMY MEDICAL CENTER  
FORT SAM HOUSTON, TEXAS 78234

1 October 1976 - 30 September 1977

Investigators:

Albert T. McManus, Jr, Captain, MSC  
Virginia C. English, MS  
Robert B. Lindberg, PhD

Reports Control Symbol MEDDH-288 (R1)

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# ABSTRACT

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Circulating endotoxin was detected in 114 of 495 burn patient blood specimens. Simultaneous blood cultures were positive in 61 of the specimens. No statistical correlation could be made between the occurrence of circulating endotoxin and positive blood culture.

Sepsis  
Endotoxin  
Humans



STUDIES OF INFECTION AND MICROBIOLOGIC SURVEILLANCE  
OF TROOPS WITH THERMAL INJURY --  
DETECTION OF ENDOTOXIN IN BURNED SOLDIERS WITH SEPSIS

Previous reports from this laboratory have indicated that demonstrable circulating endotoxin was not well correlated with clinical condition or positive blood culture (1). In that study, plasma was extracted with trichloroacetic acid. Approximately 33% of plasma samples from patients with clinical sepsis, usually with positive blood culture, gave a positive gelation reaction with this procedure. This level of sensitivity was not of the order called for if the procedure was to have diagnostic or prognostic value, nor was the specificity of the reaction unequivocal.

Recently a new assay technic has been reported to improve the recovery of plasma endotoxin (2). The basis for the technic is the absorption of endotoxin in clinical materials onto plastic beads designed for their high affinity for endotoxin. The washed beads are then examined for absorbed endotoxin by exposure to limulus amoebocyte lysate.

We have prospectively examined burn patient plasma using this technic. Laboratory technicians performing the assays were unaware of the clinical conditions of individual patients. Circulating endotoxin was measured by the limulus amoebocyte bead assay (PSI 100<sup>R</sup>) in 495 specimens obtained during the intensive phase of care in 25 consecutive patients admitted for burn injury. Simultaneous blood cultures were obtained with each specimen and processed in the clinical diagnostic section of this laboratory. The test, as performed, was capable of detecting less than 0.6 nanograms of a standard commercial Escherichia coli 026:86 lipopolysaccharide.

Endotoxin concentrations of 1 ng/ml of blood or greater were detected in 114/495 specimens. Positive blood cultures occurred in 61/495 specimens. Among the isolated organisms 28 were gram positive; 31 were gram negative; 2 yeasts were identified. Circulating endotoxin and positive blood culture did not occur together in individual specimens with greater than random frequency; this random relationship also prevailed between circulating endotoxin and blood cultures positive for gram negative organisms. In addition, there was no evidence that endotoxemia preceded positive blood culture in more than a random fashion. Data are summarized in the Table. While these data indicate moderately frequent occurrence of endotoxemia and septicemia in severely burned patients, they fail to demonstrate any predictable relationship between these entities; septicemia is not predicted by endotoxemia nor is endotoxemia necessarily a concomitant of blood culture confirmed septicemia.

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1. Lindberg RB, English VC, Pruitt BA, Jr, Mason AD, Jr: Detection of endotoxin in burned soldiers with sepsis. USA Inst Surg Res Annual Rpt FY 73. Brooke Army Medical Center, Fort Sam Houston, Tx. Section 6.

2. Harris NS, Feinstein R: A new limulus assay for the detection of endotoxin. J Trauma 17:714, 1977.

Summary Table

Patient	Age	Sex	Burn Size (%)	Survival	Examined Specimens (No.)	ET Positive	BC	Prediction* 24 Hr	48 Hr
1	26	M	53	-	40	0	2	0	0
2	25	F	68	+	4	0	2	0	0
3	21	M	50	-	18	4	2	1	2
4	18	M	32	-	27	8	2	2	2
5	53	M	51	-	39	7	3	1	1
6	22	M	38	-	15	5	2	0	0
7	22	M	24	-	13	3	2	0	0
8	16	M	46	-	18	2	2	0	0
9	41	M	60	+	33	8	22	8	8
10	30	M	55	+	12	3	3	2	3
11	26	M	36	-	12	3	0	0	0
12	31	M	40	+	12	2	1	0	1
13	21	M	32	-	21	1	1	0	1
14	34	M	32	-	21	3	1	0	0
15	37	M	85	+	4	0	2	0	0
16	19	M	56	-	22	3	0	0	0
17	34	M	90	+	9	0	0	0	0
18	72	M	61	+	14	0	3	0	0
19	19	M	71	-	36	10	2	1	1
20	27	M	63	+	38	14	2	0	0
21	59	M	22	-	26	6	2	1	1
22	40	M	35	-	4	0	1	0	0
23	24	M	49	-	18	10	2	0	0
24	23	F	83	+	3	0	2	0	0
25	26	M	83	+	36	22	61	2	2

ET: Endotoxin BC: Blood culture

\* Frequency at which a positive endotoxin preceded a positive blood culture by 24 or 48 hours.  
 + indicates death.

ANNUAL PROGRESS REPORT

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84 and 84,85 IN BURNED MILITARY PERSONNEL

US ARMY INSTITUTE OF SURGICAL RESEARCH  
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1 October 1976 - 30 June 1977

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Arthur D. Mason, Jr, MD  
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Phage typing of Staphylococcus aureus has shown that a long term type 84 epidemic in the burn ward was gradually replaced by a type 84,85 epidemic. After a year of predominance of phage type 84,85, strains of the two types maintained a mixed epidemic. Non-typable strains increased in incidence from 20% of all strains to 32% in 1976-1977. Abrupt fluctuations in sensitivity to antibiotic occurred, as did rapid changes from a population of type 84 to type 84,85 and back. A high level of resistance to gentamicin, methicillin, nafcillin, tobramycin and clindamycin was present at the end of the 1976-1977 observation period.

Staphylococcus  
Antibiotic  
Phage type  
Burns  
Burn infections  
Humans



STUDIES OF INFECTION AND MICROBIOLOGIC SURVEILLANCE OF  
TROOPS WITH THERMAL INJURY -- EMERGENCE OF METHICILLIN-  
RESISTANT STAPHYLOCOCCUS AUREUS TYPES 84 and 84,85 IN  
BURNED MILITARY PERSONNEL

Antibiotic resistance in Staphylococcus aureus has presented a recurrent problem in infection in burn patients. A uniquely methicillin-resistant strain populated the burn ward during 1970-1972. Since that time, significant fluctuations in antibiotic sensitivity have occurred. Methicillin-sensitive strains reappeared in 1973, but the reversion was temporary. Since that time, resistant strains have re-emerged, and linkage with aminoglycoside and tetracycline resistance has been seen. Since staphylococcal infection, in some degree, is virtually ubiquitous, study of this phenomenon is needed.

PHAGE TYPES OF STAPH. AUREUS, 1971-1977

Throughout the past decade, Staph. aureus infections in burn patients have been characterized by predominance of one to three epidemic strains at any given time. These strains were recognized by phage type. In addition to predominant strains, a large peripheral population of Staph. aureus of varying phage types has been part of the flora of the burn patients. These strains differ widely in identity and are present only in very low concentration. Since 1971, the staphylococcus population of the Institute of Surgical Research burn wards has fluctuated from a pure type 84 to a mixed type 84,85 colonization, followed by a virtually pure 84,85 epidemic. Following this sequence, 1976 and 1977 showed a reversion to a mixed 84 and 84,85 population, with type 84,85 predominant. During the past year a remarkable increase in non-typable strains has occurred. The number of additional types which are found only in low numbers has increased as well. The sequence of events with predominant types is summarized in Table 1. This covers the period 1971-1977. Earlier epidemic patterns were described in previous reports (1). Type 84 was the only numerically significant type in the population from 1971 through 1973. In that year a significant rise in incidence of type 84,85 occurred, with 5.2% of the strains having this pattern. The relatively new phage, WH-1 (now designated type 94) appeared during 1971-1974, reached a peak of incidence in 1975, then disappeared almost completely in 1976. Type 84 was replaced slowly by type 84,85 in 1973 and 1974; then in 1975 it became the major type with only 3.8% of strains being type 84. Since that time, on an annual basis, the two types have both been present in significant numbers, with type 84,85 as the predominant strain. Type 96, another relatively new addition to the typing schema, was the next new type to achieve significant numbers in burn patients, although it was still relatively uncommon. The proportion of non-typable strains was surprisingly consistent for many years, at less than 20% of isolates tested, until 1977, when for the first time a jump to 35% of

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1. Lindberg RB, Latta RL, Pruitt BA, Jr, Mason AD, Jr: Emergence of methicillin-resistant Staphylococcus type 84 in burn patients. USA Institute Surg Res Annual Rpt FY 1974. Brooke Army Medical Center, Fort Sam Houston, Texas. Section 7.

Table 1. Predominant Bacteriophage Types of  
Staphylococcus aureus, 1971-1977, ISR

Type	1971	Year and % of All Strains					1976	1977*
		1972	1973	1974	1975			
84	74.6	72.5	61.1	55.6	3.8	20.0	23.9	
84,85	0.1	0	5.2	19.2	61.3	49.7	35.3	
94 (WH-1)	0	2.1	3.5	2.3	9.5	0.8	0	
96 (D-11)	0	0.4	0	0	0	1.6	8.7	
94,96	0	0	0	0	0	0.1	0.2	
Non-typable	21.6	19.9	20.5	15.6	16.9	17.7	32.3	

\* 1977: January-July

strains tested occurred. At the same time, the number of different types recovered in very small numbers (1 to 3 strains per year) increased markedly, so that the proportion of strains of the predominant types was lower in 1977 than it had been in previous years.

#### STAPH. AUREUS PHAGE TYPES IN THE ISR BURN WARD, 1976

Since significant changes occurred in the staphylococcal population between 1976 and 1977, the type data for these years was summarized separately. Four hundred ninety strains were typed in 1976 (Table 2); most were antemortem cultures with only 72 strains from autopsies typed. Blood cultures, sputum, wounds, urine and other clinical culture sources are shown. Antemortem and post-mortem cultures both showed the predominant organism to be type 84,85. However, type 84,85 and type 84 were sufficiently close in incidence to indicate that the distribution of types in fatal burns was essentially the same as that seen in the entire burn ward population. There was no indication that a different, more virulent strain was invading burns beyond the rate consistent with the whole staphylococcus population. Type 96 among less frequently encountered types, was seen for the first time in a group of 7 strains from blood and sputum. Type 6 was seen for the first time in a small group of autopsies. Five other minor types were found at least 4 times, and there were 15 strains of infrequently seen types, none of them appearing more than 3 times in the year. These 15 types made up 4% of the total of Staph. aureus typed.

#### SEPTICEMIA AND STAPH. AUREUS

A major hazard of bacteremia due to staphylococci is the establishment of endocarditis or thrombophlebitis. The identity of blood stream isolates was hence scrutinized with especial care. The phage types of strains from positive blood cultures in 1976 are summarized in Table 3. It was noteworthy that the proportion of strains in the major phage types was higher than that of

Table 2. Bacteriophage Types of 490 Strains of Staphylococcus aureus from Clinical and Postmortem Specimens, 1976-ISR

Phage Type	<u>Antemortem</u>		<u>Postmortem</u>		<u>Total</u>	
	No.	%	No.	%	No.	%
84,85	211	50.4	33	45.8	244	49.7
84	78	18.6	20	22.7	98	20.0
Non-typable	83	19.8	4	5.5	87	17.7
96	7	1.6	1	1.3	8	1.6
6	0		14	19.4	14	2.8
94,96	5	1.1	0		5	0.1
29,52,80	5	1.1	0		5	0.1
52,52A,80,81	5	1.1	0		5	0.1
94	4	0.9	0		4	0.8
15 other types (1-3 strains each)	20	4.7	0		20	4.0
Totals	411		72		490	
Total types present:	23					

strains from the populace at large. 60.1% of strains were type 84,85, and 27.7% were type 84. The difference appeared to reflect primarily the limited number of types that appear in septicemia. There were only 5 types recovered from all blood cultures in 1976. Recall that there were 22 types recovered from patients in 1976; most of these came from respiratory tract cultures.

The chronologic sequence of invasive infection by strains of Staph. aureus merits presentation, to illustrate the flow of strains in the burn population. Table 4 shows the types of Staph. aureus and their sequence of recovery from blood in 1976. For the first 7 months, type 84,85 was the only significant type.

Table 3. Phage Types of Staphylococcus aureus from Positive Blood Cultures on 40 Burn Patients, 1976

Phage Type	No.	<u>Patients</u>	No.	<u>Strains</u>
		% of Patients		% of Total
84,85	29	72.5	65	60.1
84	13	32.5	30	27.7
Non-typable	6	15.0	8	7.4
94,96	1	2.5	1	0.9
52,52A,80,81	3	7.5	3	2.7
29,79,84	1	2.5	1	0.9

Table 4. Phage Types of *Staphylococcus aureus* from Blood  
Stream of 39 Patients, ISR, 1976 - Temporal Sequence

Month	Patient No.	No. Strains	84, 85	84	Type NT	Other Types
January	6	2	2			
	2	1	1			
February	32	1	1			
	33	3	1	2		
	41	2	2			
	46	3	3			
March	48	2	2			
	54	2	2			
	59	6	5	1		
April	82	4	4			
May	89	1	1			
	90	2	2			
	190	7	5		1	94, 96 (1 strain)
	113	5	5			
	116	1	1			
June	123	1	1			
	126	2	2			
	132	1	1			
August	156	2	2			
	161	1	1			
	162	3	3			
	164	2	1	1		
	166	2	2			
	168	1	1			
	178	1	1			
September	184	1		1		
	186	1	1	4		
	187	1				52, 52A, 80, 81 (1)
October	207	1		1		
	211	3		1	1	29, 79, 81 (1)
November	221	1	1			
	223	6	4	2		
	227	1				52, 52A, 80, 81 (1)
	229	13	7	6		
	234	12	4	6	2	
	236	1	1			
	243	1		1		
	244	1				52, 52A, 80, 81 (1)
December	254	1	1			



Only 3 strains of type 84 were collected in blood culture, 2 in February and 1 in August. There were 2 non-typables and one 94,96. Then, at the end of August, type 84 strains became predominant, and abruptly replaced the type 84,85. Only one of the latter was found in September, and they did not reappear until mid-November. An unusual occurrence in this period was the appearance of 2 strains of type 52,52A,80,81. This was the "pathogenic" type which was ubiquitous in the 1950s. It has been rare for many years.

At mid-November, type 84,85 reappeared, but type 84 also persisted. Mixed seedings occurred with equal numbers of both types recovered from tissues of 2 autopsies. The intensity of the staphylococcus epidemic lessened in December, when only one patient yielded staphylococci in blood culture.

The data on staphylococcus incidence in 1976 has been shown. Certain changes observed in the collection from the first 7 months of 1977 prompts presentation of this collection separately in Table 5. The incidence of type 85 was lower and that of type 84 somewhat higher than it was in 1976. The blood stream strains encompassed only a small number of types; this limited spectrum of infecting strains showed also in wound, biopsy, urine and autopsy specimens. Only types 84; 84,85 and 96 were recovered from these sources. There were 28 other types found. They came from sputum and Luken's tube aspirates. The number of individual types represented was far greater than had been seen in previous surveys. The number of non-typable strains also increased markedly over the several preceding years. Prior to 1977, the non-typable strains had a consistent representation of approximately 20% of strains. In 1977, the rate increased to 35% and in the later months it was even higher. Non-typables, however, came from blood and wounds as well as from sputum.

Since autopsy tissues offer the most clearcut information on the organisms associated with tissue invasion in fatal burns, the strains recovered from 36 burn autopsies in 1976-1977 were examined in detail. The data on these strains illustrate limited scope of staphylococcus involvement in these fatal burns (Table 6). Type 84,85 constituted 44.3% of all strains and type 84, 30.6%. These figures are higher than the proportion found in the total of all strains, since the dilution by a large number of non-typable strains and of multiple minor types did not occur. Non-typable strains were far less common in these tissue isolates than in the population as a whole. Those that were found were primarily from lung and wound tissues. Three minor types, not seen elsewhere, were collected from viscera. Type 6 was numerically important because of 2 patients who contributed all 14 isolates. This type has not previously appeared in circumstances justifying its categorization as a pathogen.

#### ANTIBIOTIC SENSITIVITY OF STAPHYLOCOCCUS AUREUS STRAINS, 1976-1977.

The status of staphylococcal infection as an epidemic of two major phage types in 1976-1977 in the Institute of Surgical Research has been established. These strains of infecting organisms constituted the population which has exhibited an important degree of antibiotic resistance that has characterized staphylococcus infection in the burn ward. The chronologic sequence of

Table 5. Phage Types of 263 Strains of Staphylococcus aureus from  
Clinical and Autopsy Cultures: January - July 1977

Phage Type	Blood	Sputum	Source and Number of Strains			Postmortem	Total	
			Wound	Urine, Biopsy, I. V. Tip			No.	%
84, 85	39	16	6	10		22	93	33.3
84	15	9	16	5		18	63	22.9
Non-typable	27	34	7	7		10	85	32.3
96	5	8	9	1		0	23	8.7
94, 96	0	5	0	0		0	5	0.2
52, 83A	0	5	0	0		0	5	0.2
83A, 84	0	4	0	0		0	4	0.2
Types found 1-3 times franchise	3	17	3	2		4	29	11.0
Number of types recognized:	31							

Table 6. Phage Types of *Staphylococcus aureus* from Postmortem Tissues of 36 Burn Patients, ISR, 1976-1977 (January - July)

Phage Type	Spleen	Tissue Source		Wound	Total Strains	% of Total
		Lung	Liver			
84,85	5	5	28	17	55	44.3
84	6	1	18	13	38	30.6
Non-typable	1	1	7	5	14	11.2
6	0	1	7	6	13	10.4
96	0	0	0	1	1	0.8
77	1	0	0	0	1	0.8
79,81	0	0	1	0	1	0.8
81	0	0	1	0	1	0.8

changes in antibiotic sensitivity that have accompanied these epidemic strains are shown in Table 7. The data on sensitivity were extended through November, 1977, but phage typing data were only complete through July. It is important to emphasize that the antibiotic sensitivity data is derived from blood stream isolates, with only a small number of strains from other sources. Hence, the data for 1972 through 1974 are primarily type 84 data; in 1975 it is largely the sensitivity of type 84,85; and in 1976, primarily 84,85 data (60% of strains) with 27% of strains being type 84. Gentamicin, after a period when resistance was common, had one year, 1974, in which most strains were sensitive, but from 1975 on, gentamicin resistance has been present in from 50% to 70% of strains. At the end of 1977, gentamicin resistance was very high. The other aminoglycoside, tobramycin, was effective through 1976, but then dropped in parallel with gentamicin. Tetracycline resistance as shown in minocin and vibramycin effectiveness, has not appeared and persisted. Methicillin, after its low point of being effective with only 13% of strains in 1972, reached a point where 65% of strains were sensitive in 1974, but the resistance pattern reappeared in 1975, and after 2 years with extensive resistance present, the strains collected at the end of 1977 were almost entirely resistant. Oxacillin originally was parallel to methicillin in 1972, but when methicillin resistance reappeared, oxacillin did not parallel the emerging resistant pattern. Nafcillin was the most effective member of this group in 1972, and resistance did not reappear until 1976. At that time, 49% of strains were still sensitive. It fell abruptly to being totally ineffective in 1977. Sensitivity to Keflin fell to a low of 23% of strains in 1972, but this level rose progressively until in 1977 it was 100% effective *in vitro*. Clindamycin was highly effective for 4 years, but in 1977 resistant strains reached the 50% mark.

Comparison of all sensitivity tests with tests only of phage types 84 and 84,85 in 1976 showed both types to be in a comparable range with regard to gentamicin, minocin, Keflin, vancomycin, vibramycin, tobramycin and cleocin. With methicillin, type 84 strains were 31% sensitive, but of type 84,95 strains, only 11% were sensitive. Similarly, type 84 strains were all

Table 7. Antibiotic Sensitivity of *Staphylococcus aureus*: % of Strains Inhibited by 6.25 ug/ml or less: 1972-1977

Year	G	M	Antibiotic and % of Strains Inhibited by 6.25 ug/ml							
			Sc	Ps	U	Kf	Va	Vb	To	Cl
1972	35	-	13	19	26	23	-	-	-	-
1973	68	84	50	70	62	72	-	-	-	41
1974	93	96	65	83	83	90	-	-	-	96
1975	39	46	22	74	86	97	100	78	89	98
1976	50	93	23	70	49	95	100	94	100	96
1977	31	94	36	65	2	97	100	97	65	97
(Jan-Sept)										
1977	5	99	4	51	0	100	98.6	78	12	48
(Oct-Nov)										

G: Gentamicin  
M: Minocin  
Sc: Methicillin  
Ps: Oxacillin  
U: Nafcillin  
Kf: Keflin  
Va: Vancomycin  
Vb: Vibromycin  
To: Tobramycin  
Cl: Clindamycin



sensitive to oxacillin, but only 68% of 84,85 strains were sensitive. The difference with unipen was strikingly reversed: 10% of strains of 84 were sensitive, but 74% of 84,85 were sensitive. These levels are summarized in Table 8.

Table 8. Methicillin Group Sensitivities of Predominant Staph. Phage Types, 1976.

Phage type	Antibiotic and % Inhibited by 6.25 ug/ml		
	Sc	Ps	U
84	31	100	10
84,85	11	68	74

---

Sc: Methicillin;      Ps: Oxacillin;      U: Unipen

The information conveyed by detailed matching of phage type with sensitivity was unexpected, and adds importance to such detailed differentiation of strains of an epidemic species. A significantly smaller number of type 84,85 strains were sensitive to methicillin than was the case with type 84. Conversely, type 84,85 strains were far more sensitive to nafcillin than were strains of type 84. The overall totals of sensitivity of isolates during this period observed the striking differences which existed between strains of the two phage types.

Staph. aureus strains have thus been shown to be extremely labile with reference to the methicillin group of antibiotics. In addition, resistance to aminoglycosides and to tetracyclines may fluctuate widely, with or without evidence of linked resistance. These changes have occurred in this species in one phage type while a second type may retain or even exhibit an inverted resistance pattern. Detailed strain assessment is essential if monitoring of sensitivity to antibiotics is to be used effectively.

#### PRESENTATIONS

Lindberg, RB: Application of phage typing to monitoring of clinical infection. Presented at Am Soc Microbiol. Seminar on "Pseudomonas and Nosocomial Infections", New Orleans, La. May 1977.

#### PUBLICATIONS

None

ANNUAL PROGRESS REPORT

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POTENTIAL OPPORTUNISTIC PATHOGENS

US Army Institute of Surgical Research, Brooke Army Medical Center, Fort  
Sam Houston, Texas 78234

Period covered in this report: 1 October 1976 - 30 September 1977

Investigators: Robert B. Lindberg, PhD  
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Reports Control Symbol MEDDH-288 (R1)

Oxidative non-fermenting gram-negative bacteria include many species of negligible pathogenic potential, and also species such as Pseudomonas aeruginosa with auspicious potential as opportunistic invaders. Most of these species are seldom recovered in routine clinical microbiology, but special technics make isolation possible, and a series of patients was studied, primarily at autopsy, to recover such fastidious strains. Twenty-five patients yielded 74 isolates of 12 different species, including Pseudomonas maltophilia and Acinetobacter calcoaceticus. Highest concentrations were found in lung, but wounds and liver were also fruitful sources for isolation. Thirty per cent of autopsies yielded unusual species; routine technics fails to recover them. Their potential for opportunistic burn invasion and sepsis is real.

Burns  
Oxidative bacteria  
Pseudomonas  
Acinetobacter  
Flavobacterium

STUDIES OF INFECTION AND MICROBIOLOGIC SURVEILLANCE  
OF TROOPS WITH THERMAL INJURY -- NON-FERMENTATIVE  
GRAM-NEGATIVE BACILLI IN BURNED SOLDIERS:  
NEW POTENTIAL OPPORTUNISTIC PATHOGENS

Burn wound infections are usually caused by opportunistic organisms. With the exception of Staphylococcus aureus, which is primarily a pathogenic species, the major infecting organisms in burns are Enterobacteriaceae and Pseudomonas aeruginosa. However, careful study of burn wound flora has suggested that there are other opportunistic species, both fermentative organisms and oxidative, that are capable of proliferating in burn wounds and reaching the status of predominant organisms in tissues. Detection of this group of seldom noted species requires special technic and attention to detail in use of an optimal spectrum of differentiating media. This area was investigated first by English and Lindberg (1) and was followed in 1974-1975 with comparable results. These uncommon species in general required prolonged incubation in primary pour plates, thorough canvassing of such plates for a complete selection of all morphologically distinctive colonies and an extended battery of substrates for characterization of what were frequently fastidious strains. Routine culture technics evidently miss many of these strains, whose detection has increased our knowledge of the extent of bacterial colonization that is possible in the burn wound. An ultimate reason for seeking and identifying these unusual opportunists is that one of these species may at any time expand its scope of colonization and assume the attributes of a major pathogenic opportunist. The fact that, for example, Pseudomonas maltophilia has been observed as the predominant organism in viscera and wounds of burn fatalities whose antemortem course included Ps. maltophilia septicemia points to the invasive potential that resides in this frequently unsuspected population.

UNUSUAL GRAM-NEGATIVE BACILLI ENCOUNTERED IN 1976-1977.

The technic of diluting homogenized tissue which is used in quantitative biopsy and autopsy offers an optimal basis for recovery of unusual species of bacteria. Extended incubation - up to 96 or 120 hours - resulted in appearance of slow-growing fastidious strains. Deep colonies were often the source of the isolates. The highest dilution plate showing growth was used as a source for detailed definitive recovery of all species present. The results presented here therefore reflect the presence, not of relatively scarce organisms recovered from the predominant species, but in most instances the predominant species in these samples. The significance of these exotic species is enhanced when their relative density in those tissues from which were derived is considered.

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1. English VC, Lindberg RB: Non-fermentative gram-negative bacilli in burned soldiers: New potential opportunistic pathogens. USA Institute of Surgical Research Annual Rpt FY 1975. Brooke Army Medical Center, Fort Sam Houston, Texas. pp. 187-195.



Table 1 summarizes the incidence of unusual gram-negative species from a series of 82 autopsies in which definitive search was conducted. Thirty per cent of this group harbored one or more of the species collectively regarded as unusual in burn wounds. It is to be emphasized that these strains were primarily predominant in the tissues from which they were recovered. This is a relatively high incidence for species which have not been noted on routine culturing. There was no striking preponderance of any species in terms of patients positive, 7 patients harbored Flavobacterium sp., 5 Pseudomonas fluorescens and 4 Ps. maltophilia. In a previous study, Ps. maltophilia was most frequently represented. The category of unusual gram-negative bacilli included, in this observation period, fermentative species not previously recovered from burn tissues or autopsies. Enterobacter agglomerans, Klebsiella ozaenae, Serratia liquefaciens and two species of Citrobacter were included in this compilation, since their appearance in autopsy samples was even less common than that of the pseudomonads and other oxidative forms. The greater proportion of isolates were collected from lung samples, as opposed to the burn wound. Eight species were recovered from liver samples from 9 of the 25 patients at autopsy. Liver and spleen positive cultures reflect the bacteremia present terminally. There were four patients, one with Ps. maltophilia, two with Ps. fluorescens and one with Citrobacter diversus, in whom lung, liver and wound were all positive. In one, Ps. maltophilia was found in lung and wound. In four patients, one each with Acinetobacter, Klebsiella ozaenae, S. liquefaciens and Citro. diversus, the lung and liver cultures were positive. With Pseudomonas acidovorans, Moraxella osloensis and Flavobacterium sp, only the lung was positive. The lung appeared to be the most common site for colonization with these unusual opportunistic invading species. A more detailed picture of the extent of multiple species involvement occurring here is shown in Table 2, in which four selected patients with multiple infections are presented. It has been observed that patients harboring any of these unusual species are especially prone to exhibit complex mixed populations of gram-negative species.

Those patients with multiple populations of oxidative species in their tissues are shown in Table 3. The preponderance of lung involvement is shown clearly here.

No clearcut epidemic of oxidative organisms was observed, but the periods of recovery came in clusters, rather than being distributed uniformly over the observation period. These clusters of unusual wound bacteria are not directly related, in terms of bacteria involved, but it has been observed on successive studies that when one unusual species appears in wounds or in autopsy tissues, others will be recovered at the same time.

A potential for new problems in opportunistic infection in burns may well lie in this group of unusual burn microorganisms.

#### PRESENTATIONS

English VC. Oxidative bacterial species in wound infections. Nat'l meeting of Am Soc Med. Tech., Boston, Mass. 25 May 1977.

Table 1. Unusual Gram-Negative Species Recovered  
from Post-Mortem Tissues, 1976-1977

Species	No. Patients Positive (PM)	No. Strains Isolated	No. Strains			
			Liver	Spleen	Lung	Wound
<i>Ps. maltophilia</i>	4	11	3	0	7	1
<i>Ps. fluorescens</i>	5	21	2	1	7	11
<i>Ps. acidovorans</i>	1	3	0	0	3	0
<i>Moraxella osloensis</i>	1	1	0	0	1	0
<i>Acinetobacter calcoaceticus</i>	3	6	1	1	4	0
<i>Flavobacterium</i> sp.	7	10	0	0	10	0
<i>Flavo. meningosepticum</i>	3	4	2	2	0	0
<i>Klebsiella ozoenae</i>	3	3	1	0	2	0
<i>Enterobacter agglomerans</i>	1	1	0	0	0	1
<i>Serratia liquefaciens</i>	2	5	1	0	3	1
<i>Citrobacter freundii</i>	2	3	1	0	0	2
<i>Citrobacter diversus</i>	4	6	2	0	3	1
		74	13	4	40	17

Total patients positive for one or more species: 25

Patients with one species: 16

Patients with two species: 6

Patients with three species: 2

Patients with four species: 1

Table 2. Four Selected Patients Showing Distribution  
of Unusual Gram-Negative Organisms in Autopsy Tissues

Autopsy No.	Source	Species	No. Strains Isolated
1	Liver	Ps. maltophilia	1
	Spleen	Ps. maltophilia	1
	Lung	Ps. maltophilia	4
		Flavobacterium sp.	1
2	Lung	Kleb. ozaenae	1
		Ps. maltophilia	1
5	Liver	Kleb. ozaenae	1
		Ps. fluorescens	1
	Lung	Ps. fluorescens	1
		Acinetobacter calcoaceticus	2
	Wound	Ps. fluorescens	5
6	Liver	Ps. fluorescens	3
		Flavobacterium meningosepticum	1
		Ps. fluorescens	1
		Serratia liquefaciens	1
	Lung	Ps. maltophilia	1
		Serratia liquefaciens	2
		Ps. fluorescens	1
	Wound	Ps. maltophilia	1
		Ps. fluorescens	1
		Serratia liquefaciens	1

Table 3. Patients with Multiple Oxidative Organisms in Autopsy Tissues

Patient No.	Liver	Autopsy Sites			Wound
		Spleen	Lung		
1	Ps. maltophilia	Ps. maltophilia	Ps. maltophilia Flavobacterium	0	
5	Ps. fluorescens Kleb. ozaenae	0	Ps. fluorescens Ac. calcoaceticus	0	
7	Ps. fluorescens Flavo. meningosepticum	0	Ps. maltophilia Ps. fluorescens	Ps. maltophilia Ps. fluorescens	
23	0	0	Flavo. meningosepticum Ac. calcoaceticus	0	
25	Ac. calcoaceticus	Ac. calcoaceticus	Ac. calcoaceticus Ps. acidovorans	0	



## PUBLICATIONS

English VC, Lindberg RB: Isolation of Vibrio alginolyticus from wounds and blood of a burn patient. Am J Med Tech 40: 363, 1977.

ANNUAL PROGRESS REPORT

PROJECT NO. 3S762774A820-00, MILITARY BURN TECHNOLOGY

REPORT TITLE: STUDIES OF INFECTION AND MICROBIOLOGIC SURVEILLANCE OF  
TROOPS WITH THERMAL INJURY: CURRENT TRIAL OF ANTISERUM  
AGAINST GRAM NEGATIVE BACTERIA

US ARMY INSTITUTE OF SURGICAL RESEARCH  
BROOKE ARMY MEDICAL CENTER  
FORT SAM HOUSTON, TEXAS 78234

1 October 1976 - 30 September 1977

Investigators:

Thomas J. Lescher, M.D., Major, MC  
Elizabeth J. Ziegler, M.D.  
Truman M. Sasaki, M.D., Major, MC  
Basil A. Pruitt, Jr., M.D., Colonel, MC

Reports Control Symbol MEDDH-288(R1)

UNCLASSIFIED

# ABSTRACT

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REPORT TITLE: STUDIES OF INFECTION AND MICROBIOLOGIC SURVEILLANCE OF  
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Thermal injury disrupts the normal host response to infection. Burn wound invasion by gram negative bacteria is the major threat to the survival of these thermally injured patients. The purpose of this project is to investigate the effectiveness of an human antiserum in augmenting the patient's defense against gram negative sepsis. The human J5 E. coli 0111 antiserum has been prepared and supplied by Dr. Elizabeth Ziegler of the University of California School of Medicine, San Diego, California.

Pseudomonas  
Klebsiella  
Wound Infection  
Sepsis  
Endotoxin  
Topical chemotherapy  
Humans  
Staphylococci

STUDIES OF INFECTION AND MICROBIOLOGIC SURVEILLANCE OF TROOPS WITH  
THERMAL INJURY: CURRENT TRIAL OF ANTISERUM AGAINST GRAM NEGATIVE BACTERIA

Thermal injury disrupts the normal host response to infection. Two significant defects are (1) loss of the skin barrier to bacteria and (2) loss of the normal immunological response to infection. Burns hamper immunologic response by (1) delaying leucocyte migration (2) hindering intracellular lysis of bacteria (3) altering reticuloendothelial phagocytosis and (4) suppressing antibody production.<sup>1</sup> The altered leucocyte migration and depressed immunoglobulin patterns in burn patients have been confirmed at this institute.<sup>2,3</sup>

Both active and passive immunization have been used to augment the defective immunoglobulin system. Immunization in animal burn models results in striking improvement in mortality, especially against *Pseudomonas* burn wound infection.<sup>4,5,6,7,8,9</sup> Immunization has been used in burned patients for a number of years in an attempt to prevent burn wound sepsis. The results reported by Sachs, Alexander and Feller were optimistic but remain unconfirmed.<sup>10,11,12</sup>

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1. Munster AM: Alterations of the host defense mechanism in burns. *Surg Clin North Am* 50:1217-1225, 1970.
  2. Warden GD, Mason AD, Pruitt BA Jr: Suppression of leucocyte chemotaxis in vitro by chemotherapeutic agents used in management of thermal injuries. *Ann Surg* 181:363-369, 1975.
  3. Munster AM, Hoagland HC: Serum immunoglobulin patterns after burns. *Surg Forum* 20:76-77, 1969.
  4. Millican RC, Evans G, Markley K: Susceptibility of burned mice to *Pseudomonas aeruginosa* and protection by vaccination. *Ann Surg* 163:603-610, 1966.
  5. Jones RS: Early protection by vaccines in burns. *Br J Exp Pathol* 52:100-109, 1971.
  6. Jones RJ: Protection against *Pseudomonas aeruginosa* infection by immunization with fractions of culture filtrates of *Ps. aeruginosa*. *Br J Exp Pathol* 49:411, 1968.
  7. Jones RJ: Passive immunization against gram negative bacilli in burns. *Br J Exp Pathol* 51:53, 1970.
  8. Jones RJ, Lilly HA, Lowbury EJJ: Passive protection of mice against *Pseudomonas aeruginosa* by serum from recently vaccinated mice. *Br J Exp Pathol* 52:264, 1971.
  9. Markley K, Smallman E: Protection by vaccination against *Pseudomonas* infection after thermal injury. *J Bacteriol* 96:867, 1968.
  10. Sachs A: Active immunoprophylaxis in burns with a new multivalent vaccine. *Lancet* 2:959, 1970.
  11. Jones CE, Alexander JW, Fisher M: Clinical evaluation of *Pseudomonas* hyperimmune globulin. *J Surg Res* 14:87, 1973.
  12. Feller I, Pierson C: *Pseudomonas* vaccine and hyperimmune plasma for burned patients. *Arch Surg* 97:225, 1968.



In 1973, Ziegler et al reported on the use of antiserum against J5 mutant *E. coli* 0111 in agranulocytic rabbits infected with different types of gram negative bacteria.<sup>13</sup> The antiserum was protective against both *E. coli* and *Klebsiella*. The antiserum is prepared by using a mutant *E. coli* which lacks the cell wall side chains.

In nonmutant gram negative bacteria, the "O" side chains are attached to a "rough" cell wall. The "O" side chain gives bacterial cell walls antigenic specificity and differs between the types of gram negative bacteria. The "rough" cell wall, however, is common to these bacteria and appears to be associated with production of endotoxin. Since the J5 mutant *E. coli* 0111 lacks the "O" side chains, antisera made against this mutant theoretically should be effective against all bacteria with a "rough" cell wall. The antisera may protect against infection from many species of gram negative bacteria. This antiserum has been given to 49 patients with proven or suspected endotoxemia with no complications identified but the effectiveness of the antiserum in man has yet to be proven.<sup>14</sup>

#### PURPOSE

The effectiveness of this antiserum is to be determined by a clinical trial in patients with suspected or proven gram negative endotoxemia. The use of this material has been previously approved by the University of California at San Diego and by the U.S. Army Medical Research and Development Command who are supporting this project.

#### METHOD AND SUBJECTS

Nonimmune human serum and human J5 *E. coli* 0111 antiserum will be compared in a double blind clinical trial. Subjects consist of patients who have proven or suspected endotoxemia from gram negative infections. Patients are entered into the study if one or more of the following findings are present 1) Blood culture which grows a gram negative bacteria, 2) Biopsy which reveals gram negative bacterial burn wound invasion, 3) or a sudden clinical deterioration accompanied by hypothermia, hypotension and glucosuria. The institution of immune therapy will not alter the standard therapy for this problem. Patients are fully informed of both the risks and benefits and a written consent obtained. Results and data will be recorded without knowledge of whether nonimmune

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13. Ziegler EJ, Douglas H, Sherman JE, Davis CE, Braude AI: Treatment of *E. coli* and *Klebsiella* bacteria in agranulocytic animals with antiserum to UDP-GAL epimerase-deficient mutant. *J Immunol* 111: 433, 1973.

14. Braude AI, Ziegler EJ: The mechanism of action of endotoxin. USAISR Annual Research Progress Report, June 1975.

or immune serum has been administered.

#### Data Collection:

The data collection includes 1) primary source of the sepsis, 2) causative organisms, 3) summary of the clinical outcome, 4) predisposing conditions and 5) untoward reactions to the serum. Careful attention is paid before and after therapy to the clinical changes of certain factors such as vital signs, urine output and orientation. CBC, platelet counts and serum BUN, creatinine and glucose are followed each day for three days. However, the evaluation of the worth of this method of administration of sera will depend heavily on the final outcome i.e., survival or death. The accumulated data will be evaluated after 50 patients have been studied to determine if alterations are necessary in the protocol.

#### Preparation of Antiserum and Dosage:

The antiserum is supplied by Dr. Ziegler et al. The antiserum is obtained from paid volunteers who have been thoroughly screened for communicable diseases. The nonimmune serum is obtained from the volunteers before immunization. The immune serum is collected after immunization with the J5 E. coli 0111 antigens. The serum is given 3 ml/kg intravenously over 30 minutes. Since this is a double blind clinical trial, the participants at this Burn Unit do not know which serum has been given.

#### Toxicity

The side effects are infrequent but the possibilities include 1) transmission of hepatitis, 2) hemolytic transfusion reaction, 3) febrile reactions associated with pyrogens in the blood or equipment, 4) allergic reaction manifested by urticaria, 5) bacterial contamination of the plasma.

To avoid these problems, the blood is prepared from healthy volunteers who have been screened for communicable disease e.g., hepatitis and syphilis. The blood is collected aseptically, and the serum processed and stored at 4°C. A sample from each donor unit is cultured aerobically and anaerobically. Pyrogenicity is tested by injection of 3 cc of plasma intravenously into each of three rabbits. The type and Rh are recorded so that each patient will receive only appropriate sera. The risk associated with administration of this serum should not be greater than giving fresh frozen plasma. This serum has been given 57 times without evident toxicity.

#### RESULTS

To date we have had 17 patients who have voluntarily participated in this study. One patient has been entered twice; there have been 18

trials in these patients. Of this group, there have been only three survivors, all of whom have had evidence of gram negative septicemia. At least 12 of these patients died with evidence of bacteremia in an average of 7.8 days after receiving the serum.

We are not able to comment on the results of the J5 antiserum study as the double blind code has not yet been broken.

#### PRESENTATIONS

None.

RESEARCH AND TECHNOLOGY WORK UNIT SUMMARY				1. AGENCY ACCESSION <sup>a</sup>	2. DATE OF SUMMARY <sup>a</sup>	REPORT CONTROL SYMBOL DD-DR&E(AR)636	
3. DATE PREV. SUM'RY	4. KIND OF SUMMARY	5. SUMMARY SCTY <sup>a</sup>	6. WORK SECURITY <sup>a</sup>	7. REGRADING <sup>a</sup>	8. DISSEM INSTR <sup>a</sup>	9. SPECIFIC DATA- CONTRACTOR ACCESS	9. LEVEL OF SUM
76 10 01	D. CHANGE	U	U	NA	NL	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	A. WORK UNIT
10. NO./CODES <sup>a</sup>	PROGRAM ELEMENT	PROJECT NUMBER	TASK AREA NUMBER	WORK UNIT NUMBER			
A. PRIMARY	62774A	35762774A820	00	114			
B. CONTRIBUTING							
C. CONTRIBUTING							
11. TITLE (Precede with Security Classification Code) <sup>a</sup> (U) Studies of Acute Renal Insufficiency and Renal Function Changes in Injured Soldiers (44)							
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17. CONTRACT/GRANT Not Applicable				18. RESOURCES ESTIMATE		19. PROFESSIONAL MAN YRS	
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b. NUMBER <sup>a</sup>				FISCAL		77	
c. TYPE:				CURRENCY		4.8	
d. KIND OF AWARD:				78		3.5	
e. AMOUNT:						114	
f. CUM. AMT.						80	
19. RESPONSIBLE DOD ORGANIZATION				20. PERFORMING ORGANIZATION			
NAME: US Army Institute of Surgical Research				NAME: US Army Institute of Surgical Research			
ADDRESS: Ft Sam Houston, Tx 78234				Internal Medicine Branch			
				ADDRESS: Ft Sam Houston, Tx 78234			
RESPONSIBLE INDIVIDUAL				PRINCIPAL INVESTIGATOR (Furnish SSAN if U.S. Academic Institution)			
NAME: Basil A Pruitt, Jr, COL, MC				NAME: Richard H Merrill, LTC, MC			
TELEPHONE: 512-221-272C				TELEPHONE: 512-221-5416			
21. GENERAL USE				SOCIAL SECURITY ACCOUNT NUMBER:			
FOREIGN INTELLIGENCE NOT CONSIDERED				ASSOCIATE INVESTIGATORS			
				NAME: Harry R Jacobson, MAJ, MC			
				NAME:			
22. KEYWORDS (Precede EACH with Security Classification Code) (U) Acute renal failure; (U) Renal physiology; (U) Renal pathology; (U) Calcium metabolism; (U) Hypocalcemia; (U) Renin; (U) Angiotensin; (U) Humans; (U) Dogs							
23. TECHNICAL OBJECTIVE, 24. APPROACH, 25. PROGRESS (Furnish individual paragraphs identified by number. Precede text of each with Security Classification Code.) 23. (U) To study mechanisms and management of acute renal failure in burned and injured soldiers. To determine cause and significance of hypocalcemia following injury and role of calcium in hypertension. To develop a non-invasive assessment of intrarenal blood flow. To determine pathogenesis and frequency of urinary tract infections in injured soldiers.  24 (U) Globin infusions are used to cause renal failure in subhuman primate model and changes in renal function measured. Dimercaptosuccinic acid is injected and kidneys scanned to determine intrarenal blood flow distribution as compared to microsphere measurements. Changes in calcium levels following burn injury are documented and related to protein changes. Effect of calcium infusion on renin-angiotensin system will be measured.  25. (U) 76 10 - 77 09 The isotope technique of studying renal blood flow was successfully evaluated in several patients. The dog was found to be an unacceptable model for the study of human vascular access xenografts. Calcium balance studies have been completed in 20 patients, the diet data is pending. No morphologic correlation between light, transmission electron, and scanning electron microscopy and the clinical course of post traumatic acute renal failure can be made. A chronic experimental animal model for the investigation of the calcium-renin interplay has been developed. Cellular immune deficiency appears to be attributable to a dialysis induced deficiency rather than a uremic toxin.							

<sup>a</sup>Available to contractors upon originator's approval.

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ANNUAL PROGRESS REPORT

PROJECT NO: 3S762774A820-00-MILITARY BURN TECHNOLOGY

REPORT TITLE: STUDIES OF ACUTE RENAL INSUFFICIENCY AND RENAL  
FUNCTION CHANGES IN INJURED SOLDIERS

CLINICAL OPERATION, METABOLIC BRANCH, RENAL SECTION, FOR  
TREATMENT OF SOLDIERS WITH RENAL FAILURE

US ARMY INSTITUTE OF SURGICAL RESEARCH  
BROOKE ARMY MEDICAL CENTER  
FORT SAM HOUSTON, TEXAS 78234

1 January 1976 - 31 December 1976

Investigators

Harry R. Jacobson, M.D., Major, MC  
Richard H. Merrill, M.D., Lieutenant Colonel, MC

Reports Control Symbol MEDDH-288 (RI)

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The ISR Renal Section performed 23 hemodialysis treatments and one peritoneal dialysis. In addition 97 urinalyses on 35 patients were performed to investigate the incidence of fungal urinary tract infection. Histological studies of kidneys from thermally injured patients with renal failure were continued via the technique of scanning electronmicroscopy. The Second Annual Brooke Army Medical Center Nephrology Seminar was held 28, 29, and 30 January 1976

Hemodialysis  
Peritoneal dialysis  
Urinary tract infection

## STUDIES OF ACUTE RENAL INSUFFICIENCY AND RENAL FUNCTION CHANGES IN INJURED SOLDIERS

### CLINICAL OPERATION, METABOLIC BRANCH, RENAL SECTION FOR TREATMENT OF SOLDIERS WITH RENAL FAILURE

The Renal Section of the ISR includes a Nephrologist and two hemodialysis technicians who also function as research technicians. The primary mission of the Renal Section is to support the Clinical Division of the ISR. This support is in the form of consultation on thermally injured patients who develop either renal insufficiency or disorders of body fluids, electrolytes or acid base disturbances. Patients who develop renal failure are dialyzed when necessary. In addition to the major mission at ISR, the Renal Section has a secondary mission to support the Nephrology Service of the Brooke Army Medical Center. Patients with renal failure at the main hospital of Brooke Army Medical Center are dialyzed by the ISR hemodialysis team. Further support of the BAMC Nephrology Service is provided by the Chief of the ISR Renal Section who participates in patient care at BAMC.

Eleven patients with renal failure were dialyzed by the ISR team. Two non-thermally injured patients were hemodialyzed a total of three times. Both survived. Nine thermally injured patients were dialyzed 20 times with all nine subsequently dying of burn wound sepsis.

In addition to consultation and hemodialysis the Renal Section has a major research commitment both with respect to clinical and more basic research. Two major clinical projects have been continued. The first is a histological study of kidney tissue obtained immediately post mortem from thermally injured patients who develop renal failure. Scanning electron microscopy is now being utilized. The study intends to answer the question of whether or not morphological changes in the glomerulus are responsible for the renal failure seen in the thermally injured. Results of this study will be presented both at the 30th Anniversary of the ISR in 1977 as well as the American Society of Nephrology in 1977.

The second clinical study involves serial urinalyses in thermally injured patients to detect fungus infection and then to determine whether the site of fungal infection is in the upper or lower urinary tract by the use of immunofluorescent antibodies. The ISR hemodialysis technicians have been trained in the immunofluorescent techniques and to date have completed 97 urinalyses on 33 patients.

In addition to these ongoing clinical studies, plans have been formulated to: 1. Perform a retrospective study on all thermally injured patients admitted to the ISR in 1976 with the intentions of identifying all patients who developed renal failure, and compare their course with patients who maintained normal renal function. From this data it is hoped that predictive and risk factors may be obtained. 2. Perform a

prospective study on thermally injured patients first to describe the changes in renal function that occur with burn injury and resuscitation (renal blood flow, glomerular filtration, osmolar clearance, fractional excretion of various solutes), and second to describe the pathophysiology when these patients develop impaired renal function.

Finally, USAISR Nephrologists coordinated the Second Annual Brooke Army Medical Center Nephrology Seminar, a three day event devoted to kidney physiology and clinical disorders of renal functions. Guest speakers from all over the United States participated. The Third Annual Seminar which will take place in 1977 will be sanctioned by the American College of Physicians as a post graduate education course.

#### PRESENTATIONS AND/OR PRESENTATIONS

None



TERMINATION

PROJECT NO. 3S762774A820-00-MILITARY BURN TECHNOLOGY

REPORT TITLE: STUDIES OF ACUTE RENAL INSUFFICIENCY AND RENAL  
FUNCTION CHANGES IN INJURED SOLDIERS

DIFFERENTIAL RENAL BLOOD FLOW IN CRITICALLY ILL THERMALLY  
INJURED PATIENTS

US ARMY INSTITUTE OF SURGICAL RESEARCH  
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1 October 1976 - 30 September 1977

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US Army Institute of Surgical Research, Brooke Army Medical Center,  
Fort Sam Houston, Texas 78234

Period covered in this report: 1 October 1976 - 30 September 1977

Investigator: William S. McDougal, Major, MC

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Four thermally injured patients received renal scans with DMSA during the early post resuscitative period. These scans were analyzed and revealed excellent flow to the kidneys. They were to serve as a baseline to be compared to scans obtained later in the patients course should renal failure develop. None of the patients developed renal failure. The project was terminated when the investigator completed his military service.

Renal Scans  
Renal Failure  
Kidneys

ANNUAL PROGRESS REPORT

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FUNCTION CHANGES IN INJURED SOLDIERS

LYOPHILIZED UMBILICAL VEINS IN THE CREATION OF A-V FISTULA IN  
THE EXPERIMENTAL ANIMAL

US ARMY INSTITUTE OF SURGICAL RESEARCH  
BROOKE ARMY MEDICAL CENTER  
FORT SAM HOUSTON, TEXAS 78234

1 October 1976 - 30 September 1977

Investigator

Richard H. Merrill, M.D., Lieutenant Colonel, MC

Reports Control Symbol MEDDH-288 (RI)

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## ABSTRACT

PROJECT NO. 3S762774A820-00-MILITARY BURN TECHNOLOGY

REPORT TITLE: STUDIES OF ACUTE RENAL INSUFFICIENCY AND  
RENAL FUNCTION CHANGES IN INJURED SOLDIERS

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IN THE EXPERIMENTAL ANIMAL

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Human umbilical cords were harvested from normal human placentas under clean conditions. The cords were placed in a sterile saline solution containing three antibiotics and were subsequently either lyophilized intact or the veins were dissected from the cord and the veins were lyophilized. These grafts were then used to create A-V fistulae in laboratory canines. The fistulae were constructed between the inner common carotid artery and jugular vein in the dog. A vein was placed on one side of the neck with an intact cord placed in the other side of the neck. In the cases where the intact cord was placed only the vein was anastomosed with the remainder of the cord providing mechanical integrity. In view of our successful use of lyophilized jugular vein allografts in the dog there was an initial high rate of graft rupture in the present study using umbilical vein xenografts. The protocol called for ten dogs to be utilized, but after five grafts were in place the high failure rate suggested that umbilical cord xenografts might not be an appropriate material for vascular access. Therefore it was elected to enter no more dogs into the study but to merely observe the remainder of the dogs for the period of one year. As the grafts have failed, the material has been saved for histologic examination as well as immunofluorescent examination. As none of the dogs have reached one year, a complete evaluation cannot be performed at this time. At one year the functioning grafts will be removed and their histology and immunofluorescent microscopy will be compared to that of the other grafts which have failed.

Dogs  
Chronic Renal Failure



ANNUAL PROGRESS REPORT

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IMMUNE DEFICIENCY IN DIALYSIS PATIENTS: A STUDY OF ACUTE  
RENAL INSUFFICIENCY AND RENAL FUNCTION CHANGES IN INJURED  
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IMMUNE DEFICIENCY IN DIALYSIS PATIENTS: A STUDY OF ACUTE RENAL INSUFFICIENCY AND RENAL FUNCTION CHANGES IN INJURED SOLDIERS

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It has been assumed that the depressed cellular immunity in patients with chronic renal failure is due to some "uremic toxin". However there are many groups of patients and clinical situations that result in a depression of cell mediated immunity but with normal renal function; among them protein-calorie malnutrition and phosphate depletion. If a uremic toxin is responsible, rather than a deficiency state, the presence of depressed cellular immunity should correlate with the degree of renal insufficiency.

Forty-three patients with end-stage renal disease on chronic hemodialysis and fifteen patients with varying degrees of renal failure on conservative management were studied. Neutrophil chemotaxis was assayed and T and B lymphocytes were enumerated. B lymphocytes were similar in both groups and not different from normals, while T cells were depressed only in the dialysis group. Chemotaxis was normal in the non-dialysis group, but was depressed in the patients on dialysis. There was no correlation between serum creatinine and chemotaxis in the non-dialysis group, but there was a tendency for chemotaxis to become more abnormal as length of time on chronic dialysis increased. Complement and immunoglobulins were normal in both groups with the exception of elevated IgE in both groups.

These data indicate that the depressed cellular immunity seen in patients with end-stage renal disease may be due to protein-calorie malnutrition or other deficiency rather than a uremic toxin.

The above data were accepted for presentation at the American Society of Nephrology Meeting in November 1977. The original protocol called for analysis for amino acid levels in dialyzed patients as well as manipulation of in vitro testing to replace demonstrated deficiencies of amino acid in

the prospect of reversing the already identified abnormal tests of cell mediated function. It has not been possible to perform the amino acid analysis at the Institute of Surgical Research, therefore the amino acid assays were sent to McGaw Company in California where the results of the assays on approximately 60 patients are pending. Since a pattern of amino acid deficiencies cannot be recognized until these data are returned, no manipulation of *in vitro* testing has been possible. It is anticipated that these data should be available shortly and the remainder of the protocol can be pursued.

#### PUBLICATIONS AND/OR PRESENTATIONS:

An abstract entitled "Depressed Cellular Immunity in Patients With Chronic Renal Failure" has been accepted for presentation in the Poster section at the 10th Annual Meeting of the American Society of Nephrology in Washington, D.C. in November 1977.

Humans  
Chronic Renal Failure  
Immune Deficiency

ANNUAL PROGRESS REPORT

PROJECT NO. 3S762774A820-00-MILITARY BURN TECHNOLOGY

REPORT TITLE: STUDIES OF ACUTE RENAL INSUFFICIENCY AND RENAL  
FUNCTION CHANGES IN INJURED SOLDIERS

EVALUATION OF CALCIUM METABOLISM IN BURNED TROOPS

US ARMY INSTITUTE OF SURGICAL RESEARCH  
BROOKE ARMY MEDICAL CENTER  
FORT SAM HOUSTON, TEXAS 78234

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The mechanism of hypocalcemia and hypophosphotemia early in the course of thermally injured patients was studied in twenty patients. Although the balance studies have been completed for some period of time the diet data are not available on the entire twenty patients. The data are undergoing processing at this time and it is anticipated that the remainder of the diet data will be available before the first of the calendar year. The urinary cyclic AMPs have been performed on all specimens and are exceedingly high. The serum parathormone levels have not yet been analyzed by Dr. Goldsmith, but await the complete analysis of the balance and diet data. It is anticipated that the analysis and tabulation of the data on this protocol will be completed this year.

Humans  
Acute renal failure  
Hypocalcemia

ANNUAL PROGRESS REPORT

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RENAL FUNCTION IN THE BURNED SOLDIER I. HISTOLOGY

US ARMY INSTITUTE OF SURGICAL RESEARCH  
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1 October 1976 - 30 September 1977

Investigators

William D. Myers, M.D., Lieutenant Colonel, MC  
Richard H. Merrill, M.D., Lieutenant Colonel, MC  
Paulette C. Langlinais, MS

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## ABSTRACT

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The pathophysiology of non-oliguric renal failure seen in patients with thermal injury is unknown. It is characterized by azotemia, low urine sodium, but adequate urine output. Hypotension, immune complex nephritis, obstruction and disseminated intravascular coagulation could be eliminated. Immunofluorescent and transmission electron microscopy on post mortem kidney tissue was normal. Because experimental studies in animals have suggested that surface alterations in glomeruli might be correlated with several models of renal failure, 16 patients with severe thermal injury coming to post mortem examination were studied.

On the basis of clinical data and routine chemistries, patients were separated into 4 groups: (1) those with normal renal function ( $U_{cr}/Scr > 20$ ,  $U_{Na} > 10$  mEq/L), (2) those with prerenal azotemia ( $U_{cr}/Scr > 20$ ,  $U_{Na} < 10$  mEq/L), (3) those with "burn azotemia" ( $U_{cr}/Scr < 20$ ,  $U_{Na} < 10$  mEq/L) and those with classic acute renal failure ( $U_{cr}/Scr < 20$ ,  $U_{Na} > 20$  mEq/L). Although the glomerular alterations described in the animal models were seen, the groups could not be separated based on scanning electron microscopy findings.

It is concluded that glomerular surface alterations presumably reflecting glomerular filtration dynamics do not explain the diminished glomerular filtration rate in the face of normal urine volumes seen in the thermally injured patient.

Humans  
Acute Renal Failure  
Renal Pathology

## STUDIES OF ACUTE RENAL INSUFFICIENCY AND RENAL FUNCTION CHANGES IN INJURED SOLDIERS

### RENAL FUNCTION IN THE BURNED SOLDIER, I. HISTOLOGY

#### INTRODUCTION

The pathophysiology of acute renal insufficiency in man remains an enigma despite the various experimental animal models of acute renal failure. One of the obstacles to better understanding of the acute renal syndrome in man is the small number of patients developing renal insufficiency at any one institution. The thermally injured patient still has a relatively high incidence of acute renal insufficiency although markedly improved with better resuscitative techniques. The most frequent form of acute renal insufficiency observed in the thermally injured patient is manifested by a BUN rising out of proportion to the serum creatinine, daily urine volume greater than 1000 cc's, urinary sodium less than 10 mEq/L, urinary potassium greater than 40 mEq/L and a urine creatinine to serum creatinine ratio which progressively falls to below 20. Observing this pattern in 1959 Graber and Sevitt suggested that the observed renal insufficiency was due to glomerular dysfunction rather than tubular disease. Morphologically, they supported their thesis by observing little correlation between tubular morphology and renal function. They suggested that the glomerulus should be evaluated more closely in man since mild morphologic abnormalities were thought to be observed. Recently, there has been a renewed interest in the role of the glomerulus in acute renal insufficiency with observation of surface alterations viewed by scanning electron microscopy in animal models of acute renal failure. This paper reports glomerular alterations observed by scanning electron microscopy in thermally injured man.

#### METHODS:

Any patient on whom post mortem examination was granted so that the tissue could be obtained within an hour of death was entered into the study regardless of kidney function. Tissue was obtained by percutaneous needle biopsy and immediately placed in 2.5% glutaraldehyde. Renal biopsies for scanning electron microscopy were fixed in 2.5% glutaraldehyde in 0.1 M sodium cacodylate buffer, pH 7.3 for 4 to 24 hours at 4°C. Fixed specimens were washed in buffer, dehydrated in graded ethanol/water solutions to absolute ethanol, then through graded ethanol/Freon-113 solutions to absolute Freon-113, into Freon-13 from which it was dried by the critical-point method in a Bomar SPC 900. After critical-point drying the specimens were mounted on aluminum stubs using electrically conducting silver paint. The secured specimens were coated in a HUMMER II D C Sputtering system with 150 Å of gold/palladium and examined in a ETEC Autoscan at either 10 or 20 KV.



Patient's were placed into one of four categories based on studies performed during routine medical management. The majority of urinary values were obtained from "spot urines" rather than 24-hour collections. Patient's were assigned to the categories based on the last day that complete values were available which did not always correspond to the day of death. The conventionally selected categories were: (1) Normal (urine creatinine to serum creatinine ratio greater than 20, urine sodium greater than 10 mEq/L), (2) Prerenal (urine creatinine to serum creatinine ratio greater than 20, urinary sodium less than 10 mEq/L), (3) Burn Azotemia (urine creatinine to serum creatinine ratio less than 20, urine sodium less than 10 mEq/L), and (4) Classic Acute Renal Failure (urine creatinine to serum creatinine ratio less than 20, urinary sodium greater than 20 mEq/L).

## RESULTS

Sixteen patients were studied. Table I summarizes the clinical data which was used to find the patient groups. Most lab studies were collected the day of death or the day preceding. However, in 4 patients data was incomplete within 24-hours of death and patients had to be grouped by most recent complete data. Frequently, gross changes in clinical data were observed within 24-hours of death as illustrated by CP in group 3 who had a 24-hour urine output in excess of 4 liters on day preceding death. Patient RD in group 1 died within 24-hours of his burns and insufficient data was collected. However, his UUN to BUN ratio of 30 and urine specific gravity of 1.019 were used to place him in group 1. SD in group 2 was deemed unsalvageable and for this reason, lab data collection was stopped. In patient DS of group 2, urinary sodium was not reported so urinary chloride was used to categorize this patient.

Table II summarizes the histologic observations by a clinical group. The scanning electron micrograph interpretations are very subjective. Only glomeruli were examined by scanning electron microscopy and their number range from 1 to 7. Generalized abnormality refers to one glomerulus being totally abnormally. Segmental abnormality is used when only a portion of a glomerulus is abnormal. Melting is purely a descriptive term and is selected to describe epithelial cells and podocytes which have lost sharp margination and can best be compared to a wax form losing integrity with heat. Disorganization is used to describe the loss of symmetry of interdigitating foot processes in contrast to melting where symmetry is maintained if one can define the margins. Retraction refers to shrinking of foot processes, Villi are microprojections from epithelial cells and podocytes surfaces which project like tiny fingers. Sponging describes alterations of epithelial cell surface which look like the surface of a fine kitchen sponge. The light microscopic findings are as stated and the lack of correlation between clinical syndromes, light microscopy and scanning electron microscopy is obvious.

TABLE I

PATIENT	% BURN	Ucr	Scr	Upc	U Volume	DAYS PRECEDING DEATH	AGE
GROUP I							
AJ	53	68	2.2	30	1241	1	26
WS	41	128	1.1	15	1774	2	46
RD	50		0.6	76	322	0	27
GROUP II							
SD	86	90	0.7	1		7	22
AH	60	98	1.4	8	786	1	79
WC	33.5	60	1.2	1	467	0	50
DS	65	116	1.9	(Uc1 1)	775	0	21
TF	54.5	130	1.6	8	1060	0	21
GROUP III							
PW	70	26	1.5	2	852	3	6
CP	36	60	3.2	7	66	0	59
JG	66.5	46	2.5	7	1325	2	25
GROUP IV							
SW	34.5	12	4.3	96	329	1	2
GL	20	176	9.6	34	41	1	74
MW	56	40	6	91	402	1	22
JF	54	26	5.6	17	49	0	44
RM	54.5	34	5.6	26	458	1	33

TABLE II

PATIENT	HISTOLOGY	SCANNING
<b>GROUP I</b>		
AJ	Cell Infiltrate, WNL	Seg. Melt., Disorg., Retraction
WS	Cortical Infarct	Mild Seg. Melt.
RD	ATN	Spongy Podocyte Body
<b>GROUP II</b>		
SD	Early ATN	Mod. Seg. Melt., Mild Disorg.
AH	Medullary	Mod. Seg. Melt & Disorg.
WC	Interstitial Nephritis	Early Seg. Melt
DS	Glomerular Fibrosis	Severe Gen. Disorg. & Melt.
TF	WNL	Seg. Melt. & Retraction
<b>GROUP III</b>		
PW	Vas. Congest, WNL	Mod. Melt. & Disorg.
CP	Early ATN	Gen. Med. Melt. & Disorg.
JG	Vasc. Congest., WNL	Mild. Mod. Seg. Melt, Mild. Disorg.
<b>GROUP IV</b>		
SW	Normal	WNL - Many Villi & Synechiae
AL	Tubule Regen.	Mild Seg. Melt. & Disorg.
MW	ATN	Mod. Seg. Melt. & Disorg.
JF	RBC casts, WNL	Severe Seg. Melt & Loss of Org.
RM	ATN	Mild Seg. Disorg. & Melt

## DISCUSSION:

With improved resuscitative techniques of the thermally injured, classic acute renal failure has shown a great decline. However, renal dysfunction is still observed. The most frequent form of renal dysfunction is manifested by the blood urea rising out of proportion to the serum creatinine, a urine output usually greater than 1 liter/day and avid urinary retention of sodium with kaliuresis and a high urine creatinine to serum creatinine ratio which slowly falls to less than 20. Previous investigators have made these observations and used them to infer tubular necrosis as the underlying cause of acute renal failure. It is puzzling however, that a necrotic tubule could have such an avidity for sodium and secrete over 100 mEq of potassium. Graber and Sevit were unable to correlate anatomic tubular alterations with renal function and suggested that the glomerulus be more closely investigated.

An obstruction between the glomerulus and the tubule would reduce and slow the filtrate allowing for maximum time for sodium-potassium exchange. The plasma remaining within the vascular tuft would flow more rapidly through the vasa-recti causing a washout of the hypertonic interstitium which would reduce the effect of ADH and cause an inappropriate urine output. Earlier it was asked if fibrin deposition, immune complex deposition, or basement membrane alteration might explain the clinical presentation. However, our study failed to show fibrin or immune complex deposition by immunofluorescent or transmission electron microscopy. And, no consistent basement membrane alteration could be correlated with renal function. Furthermore, urinary fibrin split products did not correlate

Alteration of the glomerular surface has been observed by scanning electron microscopy in experimentally induced acute renal failure in the rat. However, this surface alteration was used to explain the oliguria observed in acute renal failure. Our study suggests that there is no correlation between scanning electron microscopic changes and renal function in man. Although the groups were defined by clinical lab values, it is important to note that 50% of the patients in the classic acute renal failure group had normal or minimal changes of the glomerular surface by scanning electron microscopy, yet 2 of the 3 were signed out as having acute tubular necrosis by light microscopy. This would suggest that glomerular surface changes do not play a major role in causing oliguria in acute renal failure in man.

No consistent glomerular surface alteration by scanning electron microscopy was observed in group 3, the burn syndrome, to explain the renal dysfunction. Comparing all of the scanning micrographs, one is unable to separate the clinical groups, which suggest that the glomerular alteration cannot be used to explain the renal function alterations observed in man.



ANNUAL PROGRESS REPORT

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THE EFFECTS OF CALCIUM ON THE RENIN-ANGIOTENSIN SYSTEM-USE OF  
AN ANIMAL MODEL OF HYPERTENSION

U.S. ARMY INSTITUTE OF SURGICAL RESEARCH  
BROOKE ARMY MEDICAL CENTER  
FORT SAM HOUSTON, TEXAS 78234

1 October 1976 - 30 September 1977

Investigator

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William D. Myers, M.D., Lieutenant Colonel, MC  
Thomas J. Lescher, M.D., Major, MC

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The completion of this protocol to assess the effect of calcium infusion in the renal artery on the Renin-Angiotensin System has been delayed awaiting the perfection of a chronic awake intact animal model. Such a model has been successfully completed with a few minor technical problems to be solved. It is anticipated that the protocol can be successfully completed within this coming year and that this model will form an important nucleus for further chronic clearance studies of the *genesis of renal failure* in the burned soldier.

Dog  
Calcium metabolism  
Renin-Angiotensin  
Renal Physiology

RESEARCH AND TECHNOLOGY WORK UNIT SUMMARY				1. AGENCY ACCESSION <sup>a</sup>	2. DATE OF SUMMARY <sup>a</sup>	REPORT CONTROL SYMBOL DD-DR&E(AR)636	
3. DATE PREV. SUMRY 77 10 01	4. KIND OF SUMMARY D. CHANGE	5. SUMMARY SCTY <sup>a</sup> U	6. WORK SECURITY <sup>a</sup> U	7. REGRADING <sup>a</sup> NA	8. DISSEM INSTR <sup>a</sup> NL	9b. SPECIFIC DATA- CONTRACTOR ACCESS <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	
10. NO./CODES <sup>a</sup>		PROGRAM ELEMENT	PROJECT NUMBER	TASK AREA NUMBER	WORK UNIT NUMBER		
a. PRIMARY		61101A	3A161101A91C	00	090		
b. CONTRIBUTING							
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11. TITLE (Precede with Security Classification Code) <sup>a</sup> (U) Measurement of Pulmonary Tissue Volume in Thermally Injured Soldiers (44)							
12. SCIENTIFIC AND TECHNOLOGICAL AREAS <sup>a</sup> 003500 Clinical Medicine							
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17. CONTRACT/GRANT Not Applicable				18. RESOURCES ESTIMATE		a. PROFESSIONAL MAN YRS	
a. DATES/EFFECTIVE:				PRECEDING		b. FUNDS (In thousands)	
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c. TYPE:				CURRENT		78 .7 30	
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19. RESPONSIBLE DOD ORGANIZATION				20. PERFORMING ORGANIZATION			
NAME: US Army Institute of Surgical Research				NAME: US Army Institute of Surgical Research			
ADDRESS: Fort Sam Houston, Texas 78234				ADDRESS: Pulmonary Section Fort Sam Houston, Texas 78234			
RESPONSIBLE INDIVIDUAL				PRINCIPAL INVESTIGATOR (Furnish SSAN if U.S. Academic Institution)			
NAME: Basil A. Pruitt, Jr., MD, COL, MC				NAME: Victor Lam, MAJ, MC			
TELEPHONE: 512-221-2720				TELEPHONE: 512-221-6532			
21. GENERAL USE				SOCIAL SECURITY ACCOUNT NUMBER:			
FOREIGN INTELLIGENCE NOT CONSIDERED				ASSOCIATE INVESTIGATORS			
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22. KEYWORDS (Precede EACH with Security Classification Code) <sup>a</sup> (U) Upper airway obstruction; (U) Airway management; (U) Total thoracic resistance; (U) Central airway resistance							
23. TECHNICAL OBJECTIVE, 24. APPROACH, 25. PROGRESS (Furnish individual paragraphs identified by number. Precede text of each with Security Classification Code.)							
23. (U) The military relevancy is to evaluate the significance of pulmonary extravascular lung water changes in burned soldiers and assess the effectiveness of conventional therapy.							
24. (U) With the disappearance of an indicator soluble gas during a rebreathing maneuver, pulmonary extravascular water will be determined and correlated with changes in arterial blood gas tension and body weight.							
25. (U) 77 04 - 77 09 Pulmonary extravascular lung water apparatus is operational, with standard deviations of 5% in normal subjects. Data computation is accomplished via digitizer and minicomputer. Two thermally injured patients have been studied to date, lung water values appears to correlate with clinical criteria of pulmonary edema.							

<sup>a</sup>Available to contractors upon originator's approval

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PREVIOUS EDITIONS OF THIS FORM ARE OBSOLETE. DD FORMS 1498A, 1 NOV 68 AND 1498-1, 1 MAR 68 (FOR ARMY USE) ARE OBSOLETE.

PROGRESS REPORT

PROJECT NO. 3A161101A91C-00, IN-HOUSE LABORATORY INDEPENDENT RESEARCH

REPORT TITLE: MEASUREMENT OF PULMONARY TISSUE VOLUME IN THERMALLY  
INJURED SOLDIERS

US ARMY INSTITUTE OF SURGICAL RESEARCH  
BROOKE ARMY MEDICAL CENTER  
FORT SAM HOUSTON, TEXAS 78234

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ABSTRACT

PROJECT NO. 3A161101A91C-00, IN-HOUSE LABORATORY INDEPENDENT RESEARCH

REPORT TITLE: MEASUREMENT OF PULMONARY TISSUE VOLUME IN THERMALLY  
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US Army Institute of Surgical Research, Brooke Army Medical Center,  
Fort Sam Houston, Texas 78234

Period covered in this report: 1 October 1976 - 30 September 1977

Investigators: Victor Lam, M.D., Major, MC

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Pulmonary extravascular water balance following thermal injury has been estimated by radiologic and clinical findings. Increased pulmonary capillary permeability has been implicated as an etiologic factor for the development of adult respiratory distress syndrome.

This study proposes to measure lung water by a direct, non-invasive rebreathing maneuver. Three patients have been studied to date. However, no definite conclusions can be made at this time.

Pulmonary extravascular water  
Adult respiratory distress syndrome  
Pulmonary capillary blood flow  
Pulmonary capillary permeability

## MEASUREMENT OF PULMONARY TISSUE VOLUME IN THERMALLY INJURED SOLDIERS

Alterations in pulmonary extravascular fluid balance in the thermally injured patient may be a factor in the development of adult respiratory distress syndrome. By examination of the rate of disappearance of dimethyl ether during a rebreathing maneuver, we are able to obtain a lung tissue volume (1). This noninvasive pulmonary test allows repetitive measurements that can assess the relative contribution of different therapeutic modalities on pulmonary extravascular water (2).

### METHODS AND MATERIALS

As soon as possible following the admission of an adult burned patient, pulmonary tissue volume is determined. Spirometry is obtained prior to the rebreathing maneuver. Then the subject rebreathes from a bag-in-box system, with a bag (Calibrated Instruments) containing a volume equal to FEV<sub>1</sub> of test gas mixture of 2% dimethyl ether, 10% helium, 30% oxygen, and balance nitrogen. Approximately five maximal rebreaths are obtained in 12 seconds.

Mouth concentrations of the test gases are monitored via heated inlets by a Perkin-Elmer medical mass spectrometer and recorded on a Honeywell 1858 fiberoptic recorder. Computation of data recordings is accomplished on the Hewlett-Packard 9830A minicomputer.

Data consisting of initial pulmonary patient data, arterial blood gas tensions, bronchoscopy findings, radiologic findings and lung water are collected and analyzed using programs from the Statistical Package for Social Sciences (SPSS).

### PROGRESS

The mass spectrometer and recording systems have been interfaced to provide the required 90% step response in 150 milliseconds. Modifications to the mass spectrometer for mass 15 and heated inlet system with a current limiting power supply to eliminate condensation of water vapor have caused long delays in the project.

Programming for the Hewlett-Packard 9830A minicomputer and digitizer system has allowed rapid computation of pulmonary tissue

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1. Petrini MF, Peterson BT, Hyde RW: Lung tissue volume and blood flow by rebreathing: Theory. Accepted for publication, Journal of Applied Physiology.

2. Peterson BT, Petrini MF, Hyde RW, Schreiner BF: Pulmonary tissue volume in dogs during pulmonary edema. Accepted for publication, Journal of Applied Physiology.

volume for different rebreathing rates, pulmonary capillary blood flow, and rebreathing dead space volumes.

Evaluation of a super-syringe for rebreathing measurements for patients on mechanical ventilation, elimination of the bag-in-box system with an Ohio dry spirometer to reduce apparatus dead space volume, and assessment of inequality of ventilation by rebreathing dead space volume tests are planned.

## RESULTS

In order to evaluate the reproducibility of the airway exchangeable pulmonary tissue volume measurement, two normal subjects were tested on four consecutive days, and five measurements were obtained on one day. The coefficient of variation of the measurements is 5.3%.

To date, three thermally injured patients have been studied. The pulmonary tissue volumes, body weight and alveolar-arterial oxygen gradient are listed (Table 1).

Table 1

	Days Postburn	Wt (kg)	$V_t$ (liter)	Alveolar-Arterial Oxygen Gradient (torr)
CR	1	87.72	.919	
	2	84.40	.937	
	3	83.40	1.486	
	4	82.60	1.237	
EC	2	77.90	.809	188.7
	4	71.50	.674	131.6
	6		.593	
	7		.717	
WF	0	75.60	1.251	65.7
	1	76.86	1.1115	25.6
	2	73.71	1.299	51.9
	3		.947	

At this time, no definite conclusions can be reached.

## PRESENTATIONS AND/OR PUBLICATIONS

None.

RESEARCH AND TECHNOLOGY WORK UNIT SUMMARY				1. AGENCY ACCESSION <sup>a</sup>	2. DATE OF SUMMARY <sup>a</sup>	REPORT CONTROL SYMBOL DD-DR&E(AR)535	
3. DATE PREV SUMRY	4. KIND OF SUMMARY	5. SUMMARY SCTY <sup>a</sup>	6. WORK SECURITY <sup>a</sup>	7. REGRADING <sup>a</sup>	8A. DISB'N INSTR'N	8B. SPECIFIC DATA: CONTRACTOR ACCESS	9. LEVEL OF SUM
76 10 01	D. CHANGE	U	U	NA	NL	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	A. WORK UNIT
10. NO./CODES <sup>a</sup>	PROGRAM ELEMENT	PROJECT NUMBER	TASK AREA NUMBER	WORK UNIT NUMBER			
a. PRIMARY	61101A	3A161101A91C	00	082			
b. CONTRIBUTING							
c. CONTRIBUTING							
11. TITLE (Precede with Security Classification Code) <sup>a</sup> (U) Laboratory Investigation of The Mechanisms of Acquired Leukocyte Dysfunction Following Thermal Injury in Burned Soldiers (44)							
12. SCIENTIFIC AND TECHNOLOGICAL AREAS <sup>a</sup> 003500 Clinical Medicine							
13. START DATE		14. ESTIMATED COMPLETION DATE		15. FUNDING AGENCY <sup>a</sup>		16. PERFORMANCE METHOD	
75 12		Cont		DA		C. In-House	
17. CONTRACT/GRANT Not Applicable				18. RESOURCES ESTIMATE			
a. DATES/EFFECTIVE:				a. PROFESSIONAL MAN YRS			
b. NUMBER: <sup>a</sup>				b. FUNDS (in thousands)			
c. TYPE:				PRECEDING			
d. KIND OF AWARD:				FISCAL YEAR			
e. CUM. AMT.				CURRENT			
				77 .8 26			
				78 .6 20			
19. RESPONSIBLE DOD ORGANIZATION				20. PERFORMING ORGANIZATION			
NAME: <sup>a</sup> US Army Institute of Surgical Research				NAME: <sup>a</sup> US Army Institute of Surgical Research			
ADDRESS: <sup>a</sup> Fort Sam Houston, Texas 78234				ADDRESS: <sup>a</sup> Fort Sam Houston, Texas 78234			
RESPONSIBLE INDIVIDUAL				PRINCIPAL INVESTIGATOR (Furnish SSAN if U.S. Academic Institution)			
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21. GENERAL USE				SOCIAL SECURITY ACCOUNT NUMBER:			
FOREIGN INTELLIGENCE NOT CONSIDERED				ASSOCIATE INVESTIGATORS			
				NAME: Arthur D. Mason, Jr., MD			
				NAME:			
22. KEYWORDS (Precede EACH with Security Classification Code) (U) Rat model; (U) Burns; (U) Leukocytes; (U) Glucose oxidation; (U) Latex phagocytosis							
23. TECHNICAL OBJECTIVE. <sup>a</sup> 24. APPROACH, 25. PROGRESS (Furnish individual paragraphs identified by number. Precede text of each with Security Classification Code.)							
23. (U) Efforts will be made to establish one or more metabolic basis for acquired leukocyte dysfunction following thermal injury. Establishment of specific nutritional or environmental effects may allow for corrective management.							
24. (U) Initial efforts will be to measure glucose metabolism in normal and burned patients' leukocytes. Purified and washed granulocyte populations will be examined for oxidation of Carbon 14 labeled glucose. Hexose monophosphate shunt and glycolysis activity will be estimated by release of <sup>14</sup> CO <sub>2</sub> from respectively 1- <sup>14</sup> C glucose. Measurements will be made on resting and latex particle (=0.8 μ) stimulated cells. Leukocyte function will be examined in the burned rat. Establishment of an animal model of burn associated leukocyte dysfunction will allow examination of corrective procedures <u>in vivo</u> .							
25. (U) 76 10 - 77 09 Methods to isolate rat peripheral neutrophils have been established. Assays of glucose metabolism, phagocytosis and <u>in vivo</u> chemotaxis have been established. Sixty percent burned rats have been found to have significant chemotactic depression.							

Available to contractors upon originator's approval.

DD FORM 1498  
1 MAR 66

PREVIOUS EDITIONS OF THIS FORM ARE OBSOLETE. DD FORMS 1498A, 1 NOV 65 AND 1498-1, 1 MAR 66 (FOR ARMY USE) ARE OBSOLETE.



**ANNUAL PROGRESS REPORT**

**PROJECT NO. 3A161101A91C-00, IN-HOUSE LABORATORY INDEPENDENT  
RESEARCH**

**REPORT TITLE: LABORATORY INVESTIGATION OF THE MECHANISMS OF  
ACQUIRED LEUKOCYTE DYSFUNCTION FOLLOWING THERMAL  
INJURY IN BURNED SOLDIERS**

**US ARMY INSTITUTE OF SURGICAL RESEARCH  
BROOKE ARMY MEDICAL CENTER  
FORT SAM HOUSTON, TEXAS 78234**

**1 October 1976 - 30 September 1977**

**Investigators:**

**Albert T. McManus, Jr, Captain, MSC**

**Arthur D. Mason, Jr, M.D.**

**Reports Control Symbol MEDDH-288 (R1)**

**Unclassified**

## ABSTRACT

PROJECT NO. 3A161101A91C-00, IN-HOUSE LABORATORY INDEPENDENT RESEARCH

REPORT TITLE: LABORATORY INVESTIGATION OF THE MECHANISMS OF ACQUIRED LEUKOCYTE DYSFUNCTION FOLLOWING THERMAL INJURY IN BURNED SOLDIERS

US Army Institute of Surgical Research, Brooke Army Medical Center, Fort Sam Houston, Texas 78234

Period covered in this report: 1 October 1976 - 30 September 1977

Investigators: Albert T. McManus, Jr, Captain, MSC  
Arthur D. Mason, Jr., M.D.

Reports Control Symbol MEDDH-288(R1)

Numerous reports indicate altered granulocyte function in severely burned man. During this reporting period, we have documented that glucose oxidation in granulocytes from burned patients is significantly depressed (1). The degree of depression in severely burned patients was so pronounced, that it would seem very unlikely that the cells could perform any energy dependent process in a normal manner. Additionally, burned granulocytes were hypometabolic when performing serum independent functions, e.g., phagocytosis of latex. This fact indicates that burned patient cells are intrinsically defective or are expressing a sequel of the in vivo burned environment.

In light of the extreme hormonal alterations following burn stress (2), and the known granulocyte alterations caused by those hormones (3,4), we have postulated that the previously reported granulocyte dysfunctions are stress induced (5). This hypothesis has become the major focus of experimentation.

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1. McManus AT, Jr, Lescher TJ, Mason AD, Jr, Pruitt BA, Jr: Altered human granulocyte glucose metabolism following severe thermal injury. Abst. Annual Meeting Am. Burn Assoc. 1977.

2. Wilmore DW, Long JM, Mason AD, Jr, Pruitt BA, Jr: Stress in surgical patients as a neurophysiologic reflex response. Surg Gynec Obstet 142: 25, 1976.

3. Rivkin I, Rosenblatt J, Becker EL: The role of cyclic AMP in the chemotactic responsiveness and spontaneous motility of rabbit peritoneal neutrophils. The inhibition of neutrophil movement and the elevation of cyclic AMP levels by catecholamines, prostaglandins, theophylline and cholera toxin. J Immunol 115: 1126, 1975.

4. Ignarro LJ, Cech SY: Bidirectional regulation of lysosomal enzyme secretion and phagocytosis in human neutrophils by guanosine 3'-5' monophosphate and adenosine 3', 5' monophosphate. Proc Soc Exp Biol Med 151: 448, 1976.

5. McManus AT, Jr: Current studies of leukocyte function in burn patients. Abst in publication of 30th Anniversary Program of Inst Surg Res.

Research is in progress to document the metabolic effects of burn plasma on normal granulocytes. Principal efforts are to test possible beta-adenergic effects. Cyclic nucleotide alterations are being investigated. If beta-adenergic activity is noted, corrective pharmacologic agents will be investigated in vitro. The same hypothesis is being investigated in a burned rat model (See annual report entitled "Alteration of Host Resistance in Burned Soldiers").

#### PUBLICATIONS

1. McManus AT, Jr, Lescher TJ, Mason AD, Jr, Pruitt BA, Jr: Altered human granulocyte glucose metabolism following severe thermal injury. Abstract in program for Ninth Annual Meeting American Burn Assoc., April, 1977.
2. McManus AT, Jr: Current studies of leukocyte function in burn patients. Abstract in program for 30th Anniversary Symposium for Inst Surg Res, BAMC, Ft Sam Houston, Texas. June 1977.

Rat model  
Burns  
Leukocytes  
Glucose oxidation  
Latex phagocytosis

RESEARCH AND TECHNOLOGY WORK UNIT SUMMARY				1. AGENCY ACCESSION*	2. DATE OF SUMMARY*	REPORT CONTROL SYMBOL DD-DR&E(AR)636	
3. DATE PREV. SUMMARY	4. KIND OF SUMMARY	5. SUMMARY SCTY*	6. WORK SECURITY*	7. REGRADING*	8. DISB. INSTR. N	9. SPECIFIC DATA - CONTRACTOR ACCESS	10. LEVEL OF SUM
76 10 01	H. TERM	U	U	NA	NL	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	A. WORK UNIT
10. NO./CODES*	PROGRAM ELEMENT	PROJECT NUMBER	TASK AREA NUMBER	WORK UNIT NUMBER			
a. PRIMARY	61101A	3A161101A91C	00	079			
b. CONTRIBUTING							
c. CONTRIBUTING							
11. TITLE (Precede with Security Classification Code)* (U) Development and Analysis of an Animal Model For The Post Thermal Injury Hypermetabolic Response Found in The Burned Soldier (44)							
12. SCIENTIFIC AND TECHNOLOGICAL AREAS*							
003500 Clinical Medicine							
13. START DATE		14. ESTIMATED COMPLETION DATE		15. FUNDING AGENCY		16. PERFORMANCE METHOD	
76 01		77 06		DA		C. In-House	
17. CONTRACT/GRANT Not Applicable				18. RESOURCES ESTIMATE		19. PROFESSIONAL MAN YRS	
a. DATES/EFFECTIVE:				PRECEDING		b. FUNDS (In thousands)	
b. NUMBER*				FISCAL		1	
c. TYPE:				77		18	
d. AMOUNT:				CURRENCY			
e. KIND OF AWARD:							
f. CUM. AMT.							
19. RESPONSIBLE DOD ORGANIZATION				20. PERFORMING ORGANIZATION			
NAME: US Army Institute of Surgical Research				NAME: US Army Institute of Surgical Research			
ADDRESS: Fort Sam Houston, Texas 78234				Burn Study Branch			
				ADDRESS: Fort Sam Houston, Texas 78234			
RESPONSIBLE INDIVIDUAL				PRINCIPAL INVESTIGATOR (Furnish SSAN if U.S. Academic Institution)			
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TELEPHONE: 512-221-2720				TELEPHONE: 512-221-4440			
21. GENERAL USE				SOCIAL SECURITY ACCOUNT NUMBER:			
FOREIGN INTELLIGENCE NOT CONSIDERED				ASSOCIATE INVESTIGATORS			
				NAME:			
				NAME:			
				DA			
22. KEYWORDS (Precede EACH with Security Classification Code) (U) Oxygen consumption; (U) Hypermetabolism; (U) Thermal injury; (U) Thyroid; (U) Catecholamines							
23. TECHNICAL OBJECTIVE, 24. APPROACH, 25. PROGRESS (Furnish individual paragraphs identified by number. Precede text of each with Security Classification Code.)							
<p>23. (U) To develop a reliable and easily reproducible small animal model of the postburn hypermetabolic response of humans; to better delineate the endocrine mediators of this response; to investigate the afferent mechanisms that initiate this response; to investigate the response of isolated tissues to determine which organs are hypermetabolic and which are normal or hypometabolic postburn; to better delineate the cellular mechanism of thermogenesis in the postburn hypermetabolic state.</p> <p>24. (U) Approximately 50 animals each were distributed as follows: (a) sham anesthetized, (b) burned on 50% TBS, (c) burned on 30% TBS with standard scald. These groups were prepared in growing (180 gm) rats, in adult rats (approx. 540 gm), in growing (approx. 540 gm), and adult (approx. 1000 gm) guinea pigs. Groups of 20-50% burned and 20 control adult rats were treated with endocrine blockade: (a) 2 mg/kg indomethacin (b) 1 mg/kg RO-205720, (c) 2 mg/kg meclofenamate, (d) .25 mg/kg reserpine, (e) thyroidectomy, (f) adrenalectomy. Whole body oxygen consumption was determined in modified Regnault-Reiset apparatus on each day from seven days prior to start of study to the time of burned animals complete wound healing. In vitro tissue oxygen lactate glucose and glycogen consumption or production of liver slices, diaphragm sections and white cell suspensions were made from all treatment groups at varying periods in the postburn hypermetabolic response and compared with matched controls.</p> <p>25. (U) 76 10 - 77 09 A non-temperature dependent postburn hypermetabolism of 30-40% was demonstrated in all animal types studied. The response was directly related to size of burn. Catecholamines and prostaglandins but not thyroid hormone were shown to be primary mediators of this hypermetabolic response. Increases in in vitro metabolic rate of liver and diaphragm and decreases in oxygen consumption of white cells of burned animals was demonstrated. The hypermetabolism of liver was mediated by serum factors.</p>							

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1 MAR 68

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TERMINATION REPORT

PROJECT NO. 3A161101A91C-00, IN-HOUSE LABORATORY INDEPENDENT RESEARCH

REPORT TITLE: DEVELOPMENT AND ANALYSIS OF AN ANIMAL MODEL FOR THE  
POST THERMAL INJURY HYPERMETABOLIC RESPONSE FOUND IN  
THE BURNED SOLDIER

US ARMY INSTITUTE OF SURGICAL RESEARCH  
BROOKE ARMY MEDICAL CENTER  
FORT SAM HOUSTON, TEXAS 78234

1 October 1976 - 30 September 1977

Investigators:

David N. Herndon, MD, Major, MC  
Douglas W. Wilmore, MD  
Arthur D. Mason, Jr. MD  
Basil A. Pruitt, Jr., MD, Colonel, MC

Reports Control Symbol MEDDH-288(R1)

Unclassified

# ABSTRACT

PROJECT NO. 3A161101A91C-00, IN-HOUSE LABORATORY INDEPENDENT RESEARCH

REPORT TITLE: DEVELOPMENT AND ANALYSIS OF AN ANIMAL MODEL FOR THE  
POST THERMAL INJURY HYPERMETABOLIC RESPONSE FOUND IN  
THE BURNED SOLDIER

US Army Institute of Surgical Research, Brooke Army Medical Center,  
Fort Sam Houston, Texas 78234

Investigators: David N. Herndon, MD, Major, MC  
Douglas W. Wilmore, MD  
Arthur D. Mason, Jr., MD  
Basil A. Pruitt, Jr., MD, Colonel, MC

Reports Control Symbol MEDDH-288(R1)

Thyroid hormone, prostaglandins, and catecholamines have all been considered as hormonal mediators of post-traumatic hypermetabolism. The effect of each of these hormones on oxygen consumption was evaluated by surgical ablation or pharmacologic inhibition in adult rats following 50% full-thickness scald burns.

A nontemperature dependent postburn hypermetabolism of 30-40% was demonstrated in all animal types studied. The response was directly related to size of burn. Catecholamines and prostaglandins but not thyroid hormone were shown to be primary mediators of this hypermetabolic response.

Oxygen consumption  
Hypermetabolism  
Thermal injury  
Thyroid  
Catecholamines

## DEVELOPMENT AND ANALYSIS OF AN ANIMAL MODEL FOR THE POST THERMAL INJURY HYPERMETABOLIC RESPONSE FOUND IN THE BURNED SOLDIER

Thyroid hormone, prostaglandins, and catecholamines have all been considered as hormonal mediators of post-traumatic hypermetabolism. The effect of each of these hormones on oxygen consumption was evaluated by surgical ablation or pharmacologic inhibition in adult rats following 50% full-thickness scald burns.

### METHODS

Twenty burned and 20 control 540-gm rats were studied in each treatment group. Thyroidectomies and adrenalectomies were performed one month prior to burn. All drugs were administered daily beginning seven days prior to burning. Fifty per cent scald burns were produced by placing anesthetized rats in plastic molds that allowed exposure of predetermined areas of the back and abdomen to water at 99°C for ten and four seconds, respectively. Control animals were immersed in tepid water and reclipped weekly. All animals were resuscitated with 50 ml of Harman's solution and fed ad libitum.

Oxygen consumptions were determined at four-day intervals between the seventh and 45th postburn days at an ambient temperature of  $32 \pm 1.5^\circ\text{C}$  during 1.5-hour periods in closed metabolic chambers. The volume of oxygen consumed was corrected to STPD and expressed as ml/gm/hr (1).

### RESULTS

The 50% total body surface burn resulted in a 30% to 48% increase in oxygen consumption relative to that of unburned controls in the untreated, diluent-injected, and thyroidectomized treatment groups. This post-traumatic increase in oxygen consumption was blunted to 7-15% after adrenalectomy (with or without dexamethasone replacement), to 16% with catecholamine depletion secondary to reserpine administration, and to 11% to 19% when prostaglandin synthesis or effect was inhibited with indomethacin, R02-5720 (Hoffman-LaRoche), or meclofenamate (Table 1).

### DISCUSSION

Post-traumatic hypermetabolism was significantly decreased by reduction of catecholamine output and by inhibition of prostaglandin synthesis or effect. Thyroidectomy caused a decrease in the control

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1. Farkas LG, McCain WG, Birch JR, et al: The effects of four different chamber climates on oxygen consumption and healing of severely burned rats. *J. Trauma* 13:911-916, 1973.

Table 1

Treatment Groups*	No. of Determinations		Oxygen Consumption at 32 C		% Increase	t Test P <
	Controls	Burns	Controls	Burns		
Controls, untreated	249	166	0.84 ± 0.012	1.16 ± 0.023	38	.001
Controls, injected with 1 ml diluent IV/QD	219	203	0.89 ± 0.01	1.17 ± 0.012	32	.001
Thyroidectomized	53	48	0.54 ± 0.10	0.80 ± 0.08	48	.01
Adrenalectomized	105	113	0.85 ± 0.020	0.98 ± 0.022	15	.001
Adrenalectomized + dexamethasone, 0.8 mg/ kg/day IP	51	48	0.93 ± 0.024	1.00 ± 0.022	7	.025
Reserpine, 0.25 mg/kg/ day IP	139	125	0.84 ± 0.009	0.97 ± 0.012	16	.001
Indomethacin, 2 mg/kg/ day IP	136	140	0.84 ± 0.013	0.97 ± 0.013	16	.001
RO2-5720 in 1-ml diluent IV/QD	86	85	0.94 ± 0.010	1.04 ± 0.016	11	.001
Meclofenamate in 1-ml diluent IV/QD	141	139	0.88 ± 0.014	1.05 ± 0.021	19	.001

\*IV/QD indicates intravenously every day; IP, intraperitoneally.



basal metabolic rate but did not affect the increase in oxygen consumption subsequent to thermal injury. These data suggest that catecholamines and prostaglandins, but not thyroid hormone, mediate the increase of metabolism that follows burn injury. Elevated prostaglandin concentrations have recently been found in wound exudate and lymph (2) but not blood (unpublished data) draining thermally injured tissue. The site of their participation in the hypermetabolic response to injury is unknown.

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2. Arturson, G.: Prostaglandins in human burn wound secretion. Burns 3:112-118, 1977.

#### REFERENCES

1. Farkas LG, McCain WG, Birch JR, et al: The effects of four different chamber climates on oxygen consumption and healing of severely burned rats. J. Trauma 13:911-916, 1973.
2. Arturson G: Prostaglandins in human burn-wound secretion. Burns 3:112-118, 1977.

#### PUBLICATIONS AND/OR PRESENTATIONS

Herndon DN, Wilmore DW, Mason AD Jr, Pruitt BA Jr: Humoral mediators of nontemperature-dependent hypermetabolism in 50% burned adult rats. Surgical Forum 28:37-39, 1977.

RESEARCH AND TECHNOLOGY WORK UNIT SUMMARY				1. AGENCY ACCESSION*	2. DATE OF SUMMARY*	REPORT CONTROL SYMBOL DD-DR&E(AR)636	
3. DATE PREV SUMMARY 76 10 01	4. KIND OF SUMMARY D. CHANGE	5. SUMMARY SCTY* U	6. WORK SECURITY* U	7. REGRADING* NA	8. DISB'N INSTR* NL	9. SPECIFIC DATA- CONTRACTOR ACCESS <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	10. LEVEL OF SUM A. WORK UNIT
11. NO./CODES*	PROGRAM ELEMENT	PROJECT NUMBER		TASK AREA NUMBER		WORK UNIT NUMBER	
a. PRIMARY	61101A	3A161101A91C		00		076	
b. CONTRIBUTING							
c. CONTRIBUTING							
11. TITLE (Precede with Security Classification Code)* (U) Effect of Cyclic Nucleotides on Proximal Tubular Reabsorption as an Influence on Renal Dysfunction in Injured Soldiers (44)							
12. SCIENTIFIC AND TECHNOLOGICAL AREAS* 003500 Clinical Medicine							
13. START DATE 76 10		14. ESTIMATED COMPLETION DATE Cont		15. FUNDING AGENCY DA		16. PERFORMANCE METHOD C. In-House	
17. CONTRACT/GRANT Not Applicable				18. RESOURCES ESTIMATE		19. PROFESSIONAL MAN YRS	
a. DATES/EFFECTIVE:				PRECEDING		b. FUNDS (in thousands)	
b. NUMBER:				FISCAL		77	
c. TYPE:				CURRENT		.8	
d. AMOUNT:				78		.9	
e. KIND OF AWARD:				40			
19. RESPONSIBLE DOD ORGANIZATION				20. PERFORMING ORGANIZATION			
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21. GENERAL USE				SOCIAL SECURITY ACCOUNT NUMBER:			
FOREIGN INTELLIGENCE NOT CONSIDERED				ASSOCIATE INVESTIGATORS			
				NAME:			
				NAME:			
				DA			
22. KEYWORDS (Precede EACH with Security Classification Code) (U) Cyclic nucleotides; (U) Proximal convoluted tubule; (U) In vitro microperfusion							
23. TECHNICAL OBJECTIVE,* 24. APPROACH, 25. PROGRESS (Furnish individual paragraphs identified by number. Precede text of each with Security Classification Code.)							
23. (U) The present project is designed to examine the role of cyclic nucleotides in fluid reabsorption in the proximal convoluted tubule of the kidney. Cyclic AMP may be an intermediate messenger by which various hormones (parathormone) and vasoactive substances (angiotensin, epinephrine) express their effects on proximal tubular reabsorption. It is felt that the results of this project might help us to understand the pathophysiology of altered renal function in burned patients.							
24. (U) All experiments will be conducted utilizing the technique of in vitro microperfusion of proximal convoluted tubules dissected from rabbit kidneys. Tubules are dissected, transferred to a perfusion chamber kept at 37°C and pH 7.4, hooked up specially constructed pipets where they are perfused with an ultrafiltrate of serum and bathed in serum.							
25. (U) 76 10 - 77 09 A significant number of experiments have been completed. The results to date support the hypothesis that cyclic AMP may be involved in the regulation of salt and water in the proximal tubule. Results of these experiments have been presented at a national meeting and submitted to the Journal of Clinical Investigation for publication. Further studies are being conducted to examine the exact mechanisms by which cyclic AMP changes proximal tubule permeability.							

\* Available to contractors upon originator's approval

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1 MAR 68

PREVIOUS EDITIONS OF THIS FORM ARE OBSOLETE. DD FORMS 1498A, 1 NOV 68 AND 1498-1, 1 MAR 68 (FOR ARMY USE) ARE OBSOLETE

ANNUAL PROGRESS REPORT

PROJECT NO. 3A161101A91C-00-IN-HOUSE LABORATORY INDEPENDENT  
RESEARCH

REPORT TITLE: EFFECT OF CYCLIC NUCLEOTIDES ON PROXIMAL TUBULAR  
REABSORPTION AS AN INFLUENCE ON RENAL DYSFUNCTION  
IN INJURED SOLDIERS

US ARMY INSTITUTE OF SURGICAL RESEARCH  
BROOKE ARMY MEDICAL CENTER  
FORT SAM HOUSTON, TEXAS 78234

1 October 1976 - 30 September 1977

Investigator

Harry R. Jacobson, M. D., Major, MC

Reports Control Symbol MEDDH-288 (R1)

UNCLASSIFIED



## ABSTRACT

PROJECT NO. 3A161101A91C-00-IN-HOUSE LABORATORY INDEPENDENT  
RESEARCH

REPORT TITLE: EFFECT OF CYCLIC NUCLEOTIDES ON PROXIMAL TUBULAR  
REABSORPTION AS AN INFLUENCE ON RENAL DYSFUNCTION  
IN INJURED SOLDIERS

US Army Institute of Surgical Research, Brooke Army Medical Center,  
Fort Sam Houston, Texas 78234

Investigator: Harry R. Jacobson, Major, MC

Reports Control Symbol MEDDH-288 (RI)

Under normal circumstances approximately 60% of the blood filtered in the kidney is reabsorbed by the renal proximal tubule. In normal man this represents almost 110 liters per day. Although several regulatory mechanisms have been proposed the potential role of cyclic AMP in regulating proximal tubular reabsorption has not been extensively studied. Therefore, studies were performed using the technique of *in vitro* microperfusion of nephron segments to examine the effects of a new analogue of cyclic AMP on transepithelial potential difference, net fluid reabsorption, and sucrose permeability of the isolated proximal convoluted tubule. 8-[p-chloro-phenylthio]-cyclic 3', 5'-adenosine monophosphate (Cl-PheS-cAMP), when applied to the antiluminal side of the proximal convolution in a concentration of  $10^{-5}$  M produced significant decreases in both the lumen negative transepithelial potential difference and net fluid reabsorption. Simultaneously the bath to lumen permeability to sucrose was increased.

Cyclic nucleotides  
Proximal convoluted tubule  
In vitro microperfusion

## EFFECT OF CYCLIC NUCLEOTIDES ON PROXIMAL TUBULAR REABSORPTION AS AN INFLUENCE ON RENAL DYSFUNCTION IN INJURED SOLDIERS

Studies were performed to explore the role of cyclic nucleotides in the process of volume reabsorption in the proximal convoluted tubule of the rabbit kidney.

Segments of superficial proximal convoluted tubules were dissected free-hand from a freshly prepared slice of rabbit kidney. These segments were perfused *in vitro* with an ultrafiltrate of plasma and bathed in rabbit serum maintained at 37°C and gassed with 95% O<sub>2</sub> and 5% CO<sub>2</sub> to keep pH at 7.4. Three parameters of proximal tubule transport were monitored. Transepithelial potential difference was measured by utilizing the perfusion pipet as an exploring electrode and connecting the bath to a second electrode via a Ringer's-agarose bridge. Net fluid reabsorption was measured by monitoring the rise in specific activity of radioactively labeled inulin which was present in the perfusion fluid. Finally, bath to lumen sucrose permeability was measured by observing the appearance in collected fluid of radioactively labeled sucrose which had been placed in the bath. Four sets of studies have been completed. In one group of tubules the effect of CI-PheS-cAMP on just transepithelial potential difference was measured. The lumen negative potential was observed to decrease significantly from  $-6.1 \pm 0.5$  mV (SEM) to  $-5.1 \pm 0.4$  mV with recovery to  $-6.8 \pm 0.6$  mV. In a second set of experiments transepithelial potential and fluid reabsorption were measured. Again the potential changed significantly from  $-5.8 \pm$  mV to  $-4.9 \pm 0.5$  mV while fluid reabsorption decreased significantly from  $1.77 \pm 0.08$  (SEM) nl. mm. min. to  $1.37 \pm 0.07$  nl. mm. min. In the third group of tubules both transepithelial potential and net fluid reabsorption were also measured. In addition, a recovery period was included to determine if the effects of CI-PheS-cAMP were reversible. In these tubules the lumen negative potential changed from  $-7.2 \pm 0.8$  mV to  $-5.8 \pm 0.4$  mV upon addition of  $10^{-5}$  M CI-PheS-cAMP. When this analogue of cAMP was washed from the bath the potential returned to control values of  $-7.4 \pm 0.7$  mV. Net fluid reabsorption followed a similar pattern. Control reabsorption of  $1.02 \pm 0.09$  nl. mm. min. was reduced to  $0.70 \pm 0.09$  with recovery to  $0.90 \pm 0.09$ . The last group of studies involved measurements of potential, fluid reabsorption, and bath to lumen sucrose permeability simultaneously. In response to  $10^{-5}$  M CI-PheS-cAMP the potential changed significantly from  $-5.5 \pm 0.6$  mV to  $-4.1 \pm 0.4$  mV. Fluid reabsorption decreased significantly from  $1.46 \pm 0.18$  nl. mm. min. to  $1.07 \pm 0.16$  nl. mm. min. Sucrose permeability expressed in units of  $10^{-6}$  cm. sec. increased by 100% from  $2.55 \pm 0.34$  (SEM) to  $5.02 \pm 1.3$ .

In summary CI-PheS-cAMP produces a significant decrease in both the lumen negative potential and net fluid reabsorption in the isolated perfused proximal convoluted tubule. Simultaneously, bath to lumen sucrose permeability is increased. Since it is generally accepted that sucrose trans-  
verses the proximal tubule only via extracellular routes it is concluded

that Cl-PheS-cAMP changes the paracellular pathway permeability of the proximal convoluted. Such a change in permeability would allow increased backleak of reabsorbate and thus decrease net reabsorption.

PUBLICATIONS AND/OR PRESENTATIONS:

1. Abstract was published in Clinical Research 25: 436A, 1977.
2. Manuscript entitled " The Effect of a New Analogue of Cyclic AMP on Proximal Tubule Reabsorption: Evidence for a Change in Paracellular Pathway Permeability" has been submitted to the Journal of Clinical Investigation.
3. A presentation in connection with these experiments was given in Washington, D.C. May 1977 at the American Federation for Clinical Research.

RESEARCH AND TECHNOLOGY WORK UNIT SUMMARY				1. AGENCY ACCESSION <sup>a</sup>	2. DATE OF SUMMARY <sup>a</sup>	REPORT CONTROL SYMBOL DD-DR&E(AR)636	
3. DATE PREV. SUMMARY	4. KIND OF SUMMARY	5. SUMMARY SCTY <sup>a</sup>	6. WORK SECURITY <sup>a</sup>	7. REGRADING <sup>a</sup>	8. DESIG. INSTR. <sup>a</sup>	9. SPECIFIC DATA - CONTRACTOR ACCESS <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	10. LEVEL OF SUM A. WORK UNIT
76 10 01	D. CHANGE	U	U	NA	NL		
11. NO. / CODES <sup>a</sup>		12. PROGRAM ELEMENT		13. PROJECT NUMBER		14. TASK AREA NUMBER	
A. PRIMARY		61101A		3A161101A91C		00 077	
B. CONTRIBUTING							
C. CONTRIBUTING							
15. (U) Hepatic and Muscle Membrane Kinetics in The Endotoxemic Dog: A Preliminary Study For Assessment of Membrane Function in The Septic Thermally Injured Soldier (44)							
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NAME: US Army Institute of Surgical Research				NAME: US Army Institute of Surgical Research			
ADDRESS: Fort Sam Houston, Texas 78234				ADDRESS: Fort Sam Houston, Texas 78234			
RESPONSIBLE INDIVIDUAL				PRINCIPAL INVESTIGATOR (Furnish SSAN if U.S. Academic Institution)			
NAME: Basil A. Pruitt, Jr., COL, MC				NAME: Douglas W. Wilmore, M.D.			
TELEPHONE: 512-221-2720				TELEPHONE: 512-221-4733			
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				NAME:			
				NAME:			
22. KEYWORDS (Precede EACH with Security Classification Code)							
(U) Liver; (U) Membrane transport; (U) Sepsis; (U) Indocyanine green							
23. TECHNICAL OBJECTIVE, 24. APPROACH, 25. PROGRESS (Furnish individual paragraphs identified by number. Precede text of each with Security Classification Code.)							
23. (U) To define the transport characteristics of indocyanine green in order to determine the effect of sepsis on hepatic function. To define as well through membrane potentials and intracellular ion concentrations, membrane permeability as a function of sepsis. Once having determined the appropriate transport characteristics, these techniques will be utilized in the septic thermally injured soldier to define the abnormalities and as a measure of success when corrected by various therapeutic regimens.							
24. (U) Plasma clearance and biliary secretion of indocyanine green dye were determined in 30 dogs studied before and during endotoxin administration (E. coli 0.1 mg/kg). Hepatic blood flow was monitored by Doppler flow probes dye distribution space determined by KI 131 albumin and serum chemical alterations were measured sequentially. In six of the animals glucose and insulin was administered simultaneously with the endotoxin infusion.							
25. (U) 76 10 - 77 09 Endotoxin caused a marked decrease in hepatocyte uptake and bile secretion of ICG. The impaired dye transport was not related to alterations in systemic blood pressure, splanchnic blood flow or dye distribution space. ICG uptake and biliary secretion were maintained at normal rates during endotoxin administration by simultaneous infusion of glucose and insulin.							

<sup>a</sup> Available to contractors upon originator's approval.

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ANNUAL PROGRESS REPORT

PROJECT NO. 3A161101A91C-00, IN-HOUSE LABORATORY INDEPENDENT RESEARCH

REPORT TITLE: HEPATIC AND MUSCLE MEMBRANE KINETICS IN THE ENDOTOXEMIC  
DOG: A PRELIMINARY STUDY FOR ASSESSMENT OF MEMBRANE  
FUNCTION IN THE SEPTIC THERMALLY INJURED SOLDIER

US ARMY INSTITUTE OF SURGICAL RESEARCH  
BROOKE ARMY MEDICAL CENTER  
FORT SAM HOUSTON, TEXAS 78234

1 October 1976 - 30 September 1977

Investigators:

Steven Heimbürger, MD  
W. Scott McDougal, MD, Major, MC  
Douglas W. Wilmore, MD  
Basil A. Pruitt, Jr., MD, Colonel, MC

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# ABSTRACT

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Decreased energy production, hypoglycemia, and increased cellular membrane permeability are common sequelae of endotoxemia. Because of its central role in metabolic fuel production and utilization, the liver has gained increasing attention as the primary target organ of sepsis. Standard laboratory tests of liver function often fail to reflect metabolic abnormalities of the hepatocyte. The rate of plasma clearance of indocyanine green (ICG) has been shown to be a sensitive indicator of hepatocyte function. ICG, unlike other vital dyes, does not participate in the enterohepatic circulation and is removed solely by the liver independent of renal function or hepatic lymphatic integrity. Uptake of the dye by the hepatocyte and its excretion into the bile is an energy-dependent process which can be described by enzyme kinetics. Using ICG clearance as a marker of hepatic membrane transport capability, the impact of energy substrate availability on hepatocyte transport during endotoxemia was determined.

Liver  
Membrane transport  
Sepsis  
Indocyanine green

HEPATIC AND MUSCLE MEMBRANE KINETICS IN THE ENDOTOXEMIC DOG:  
A PRELIMINARY STUDY FOR ASSESSMENT OF MEMBRANE FUNCTION  
IN THE SEPTIC THERMALLY INJURED SOLDIER

Although a variety of metabolic and circulatory events occur during gram negative bacteremia, the liver has gained increasing attention as the primary target organ during sepsis. Gram negative organisms, or their endotoxins, may decrease the aerobic capacity of the liver, impair hepatic gluconeogenesis and ketogenesis, and diminish membrane transport of substances into the hepatocyte or impair active excretion of substances in the bile. The usual laboratory tests of liver function often fail to reflect these metabolic abnormalities, and more precise measurements of hepatocyte function are needed to quantitate abnormal liver function and assess the effect of specific therapy in critically ill patients. The rate of clearance of indocyanine green (ICG) is a sensitive indicator of hepatocyte transport function. ICG, unlike other vital dyes, does not participate in the enterohepatic circulation, and is removed solely by the liver, independent of renal function or hepatic-lymphatic integrity. Uptake of the dye by the hepatocyte, and its excretion in bile, is an energy dependent process which can be described by classic enzyme kinetics.

ICG plasma dye disappearance is impaired in bacteremic, critically ill patients, and this transport function was shown to be glucose dependent. This study evaluates ICG as a clearance marker of hepatic membrane transport in an animal model where blood flow and dye distribution space can be assessed and the impact of energy substrate on hepatocyte transport determined.

Materials and Methods

Thirty-four adult conditioned mongrel dogs were studied. All animals were previously vaccinated and free of parasites and other disease. After at least 10 days of stabilization in our laboratory facility, 20 animals underwent general barbiturate-penthrane anesthesia, and, through a midline abdominal incision, two Doppler ultrasonic flow cuffs (Parks Laboratories, Beaverton, Oregon) were placed around the common hepatic artery and the portal vein. Wire leads from the flow cuffs were directed through a small stab wound in the flank and run subcutaneously to a point between the scapula on the midback. Here the wires exited through a small incision in the skin. The wires were then soldered to the female component of a small electronic jack housed within a plexiglass cylinder with a flange at its base. After satisfactory permanent electronic connection had been established, the skin incision of the back was closed around the flanged base of the cylinder. Electrical connection could thus be made with the Doppler probes through this exposed electrical plug. The abdominal wall was

closed with wire sutures and the animal allowed to stabilize for at least two weeks before study.

Following a 12-hour overnight fast, the study animals were anesthetized in the early morning. After anesthesia induction with intravenous sodium methohexital (25 mg/kg body weight), an endotracheal tube was inserted and anesthesia maintained with low concentrations of penthrane mixed with oxygen, the animal breathing spontaneously. A number 5 French polyvinyl catheter was placed in the external jugular vein and directed into the superior vena cava. A similar catheter was placed in the femoral artery and attached to a Stratham pressure transducer with blood pressure monitored continuously on a Sanborn recorder. A No. 18 catheter was placed percutaneously into an available peripheral vein in the foreleg and patency maintained with 0.9% saline. A temperature probe was placed in the esophagus to continually monitor the core temperature of the animal, which rested on a heating mattress maintained at 39°C. In the animals with the chronic flow probes, the male component of the electronic connection was attached to the exposed neck plug and appropriate leads were connected to a Model 806 Directional Doppler flow detector (Parks Laboratories). The flow signal was recorded on the Sanborn recorder.

Following a period of 10-20 minutes of stabilization of the animal following these manipulations, baseline blood samples were obtained, and ICG, 0.25 mg/kg body weight, was rapidly injected through the central venous catheter and the line flushed with sterile saline. Three ml of central venous blood were then obtained at 2, 3, 5, 8, 10, 15, 20, 25, 30, 40, 50, 60, 70, and 80 minutes following dye injection for determination of the dye disappearance rate. During this control period, and throughout the study, hepatic blood flow was measured, alternating every 15 minutes from monitoring the portal vein probe to hepatic artery probe. For each Doppler flow cuff, the precalibrated crystal oscillation frequency was used and the probe detector frequency was set to obtain the maximal or peak kilohertz signal.

The initial control study was followed by the experimental period. Twenty-two animals received *E. coli* endotoxin (*E. coli* 0.26:B6 Difco Laboratories), given as 0.1 mg/kg body weight of lipopolysaccharide followed by a 0.05 mg/kg/hr infusion for two hours via the peripheral vein cannula. Twelve control animals received equal volumes of saline without the endotoxin. Four saline controls and six endotoxin treated animals also received a bolus of 50% glucose (2 g/kg) and regular crystalline insulin (0.2 unit/kg), followed by an infusion of 0.5 g glucose/kg/hr and 0.2 unit regular insulin/kg/hr. After these infusions had been started and stabilized for approximately 15 minutes, a second dose of ICG was injected and serial samples were obtained as previously described to determine dye clearance. The previously described measurements of temperature, blood pressure,



and blood flow were continued throughout the experimental period. Arterial samples were obtained after 30 minutes of dye injection during both the control and experimental period and analyzed for pH,  $pO_2$ ,  $pCO_2$ , and glucose. At the termination of the study, the pressure transducer was calibrated with a mercury strain gauge and known frequencies were directed through the Doppler flow detector and recorded on a strip chart recorder. Peak kilohertz values were determined from these known signals.

In six additional dogs, the distribution space of ICG and albumin were measured simultaneously. The dye and 5  $\mu$ c of  $I^{131}$  albumin were injected simultaneously and serial samples obtained during 80-minute control and endotoxic experiments. The concentration of both substances was determined and the distribution space calculated as the volume required to dilute the sample to the serum concentration at time zero.

Plasma samples were centrifuged, and absorbence of each sample determined at 805  $\mu$ m with a Gilford spectrophotometer. Known concentrations of ICG prepared from the animals' plasma served as controls. The concentration of ICG in each sample was calculated directly from the standards. The rate constants for the disappearance of ICG were computer determined as previously described, with  $K_1$  representing the slope of the first component and  $K_2$  representing the slope of the second component. All curves fitted the biexponential disappearance equation with the  $r^2$  value greater than 0.9. Serum glucose values were determined by the glucose oxidase method. Blood gas values were determined by the Beckman gas analyzer. The concentration of  $I^{131}$  albumin was determined by counting the initial dose and subsequent samples in a Packard autogamma spectrophotometer, Model 3002.\*

## RESULTS

ICG plasma disappearance, performed in the endotoxin treated animals, was significantly delayed when compared with the saline-treated controls (Table 1, Fig. 1). The first rate constant,  $K_1$ , for the hepatocyte uptake of ICG, was significantly decreased following endotoxin administration, and the second rate constant,  $K_2$ , thought to reflect in part the back diffusion of ICG from the hepatocyte, was increased (Table 2). However, if the endotoxin-treated animals received glucose and insulin solution, the rate constants were unchanged from the normal control values (Fig. 2).

The alterations in clearance of ICG following endotoxin administration could be affected by hepatic blood flow or dye distribution space. However, no significant alteration was observed in hepatic

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\*Packard Instrument Co., Downers Grove, Illinois

MEAN CONCENTRATION ( $\text{mg} \pm \text{S.E.}$ ) OF ICG WITH TIME FOLLOWING A BOLUS INJECTION  
(0.25  $\text{mg/kg}$  BODY WEIGHT) UNDER VARYING EXPERIMENTAL CONDITIONS

	$\bar{n}$	Time (min)															
		2	3	5	8	10	15	20	25	30	40	50	60	70	80		
CONTROL $\pm \text{S.E.}$	39	0.543 $\pm 0.025$	0.442 $\pm 0.022$	0.359 $\pm 0.018$	0.270 $\pm 0.015$	0.208 $\pm 0.012$	0.139 $\pm 0.009$	0.095 $\pm 0.007$	0.065 $\pm 0.004$	0.054 $\pm 0.003$	0.038 $\pm 0.003$	0.033 $\pm 0.002$	0.076 $\pm 0.002$	0.075 $\pm 0.002$	0.024 $\pm 0.002$		
EMOTOXIN $\pm \text{S.E.}$	15	0.590 $\pm 0.028$	0.505 $\pm 0.025$	0.428 $\pm 0.025$	0.349 $\pm 0.021$	0.299 $\pm 0.019$	0.223 $\pm 0.017$	0.183 $\pm 0.015$	0.140 $\pm 0.013$	0.117 $\pm 0.014$	0.084 $\pm 0.009$	0.071 $\pm 0.007$	0.067 $\pm 0.005$	0.060 $\pm 0.004$	0.055 $\pm 0.004$		
CONTROL GLUCOSE AND INSULIN $\pm \text{S.E.}$	4	0.432 $\pm 0.020$	0.360 $\pm 0.017$	0.283 $\pm 0.011$	0.215 $\pm 0.008$	0.193 $\pm 0.012$	0.135 $\pm 0.009$	0.100 $\pm 0.008$	0.075 $\pm 0.005$	0.063 $\pm 0.004$	0.039 $\pm 0.005$	0.021 $\pm 0.001$	0.020 $\pm 0.002$	0.019 $\pm 0.002$	0.019 $\pm 0.002$		
EMOTOXIN GLUCOSE AND INSULIN $\pm \text{S.E.}$	6	0.447 $\pm 0.068$	0.386 $\pm 0.050$	0.316 $\pm 0.039$	0.258 $\pm 0.041$	0.202 $\pm 0.036$	0.142 $\pm 0.040$	0.125 $\pm 0.027$	0.088 $\pm 0.017$	0.070 $\pm 0.011$	0.049 $\pm 0.005$	0.039 $\pm 0.003$	0.038 $\pm 0.005$	0.034 $\pm 0.004$	0.032 $\pm 0.005$		

TABLE 1

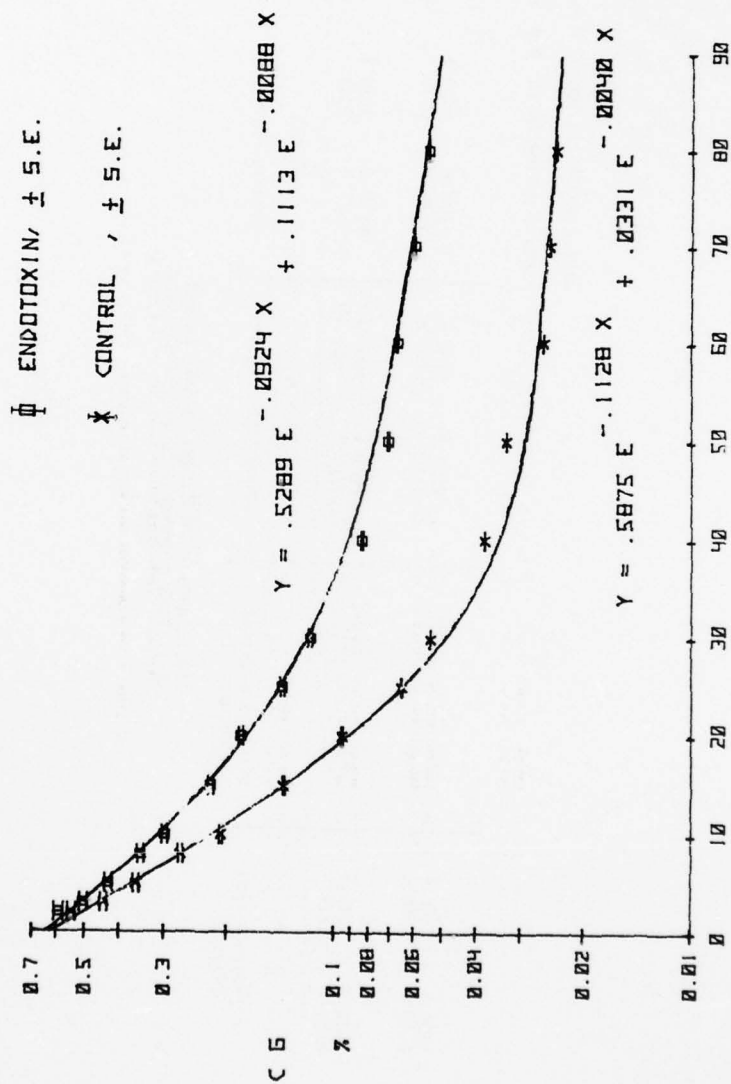


FIGURE 1

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MEAN ICG PLASMA DISAPPEARANCE RATES (+SE)  
DURING VARYING EXPERIMENTAL CONDITIONS

	Control - Control n = 8	Control - Endotoxin n = 16	Control + Gluc-Ins n = 4	Control + Gluc-Ins. n = 6
K <sub>1</sub> ± SE	- .1160 ± .0138	- .1247 ± .0087	- .1159 ± .0150	- .1123 ± .0153
	- .1346 ± .0124	- .0871*** ± .0085	- .1131 ± .0154	- .1208 ± .0180
K <sub>2</sub> ± SE	- .0052 ± .0006	- .0054 ± .0011	- .0074 ± .0011	- .0148** ± .0018
			- .0081 ± .0007	- .0069 ± .0012
				- .0053 ± .0012
				- .0063 ± .0014

\*\* p < .01 by paired t test

\*\*\* p < .001 by paired t test

TABLE 2

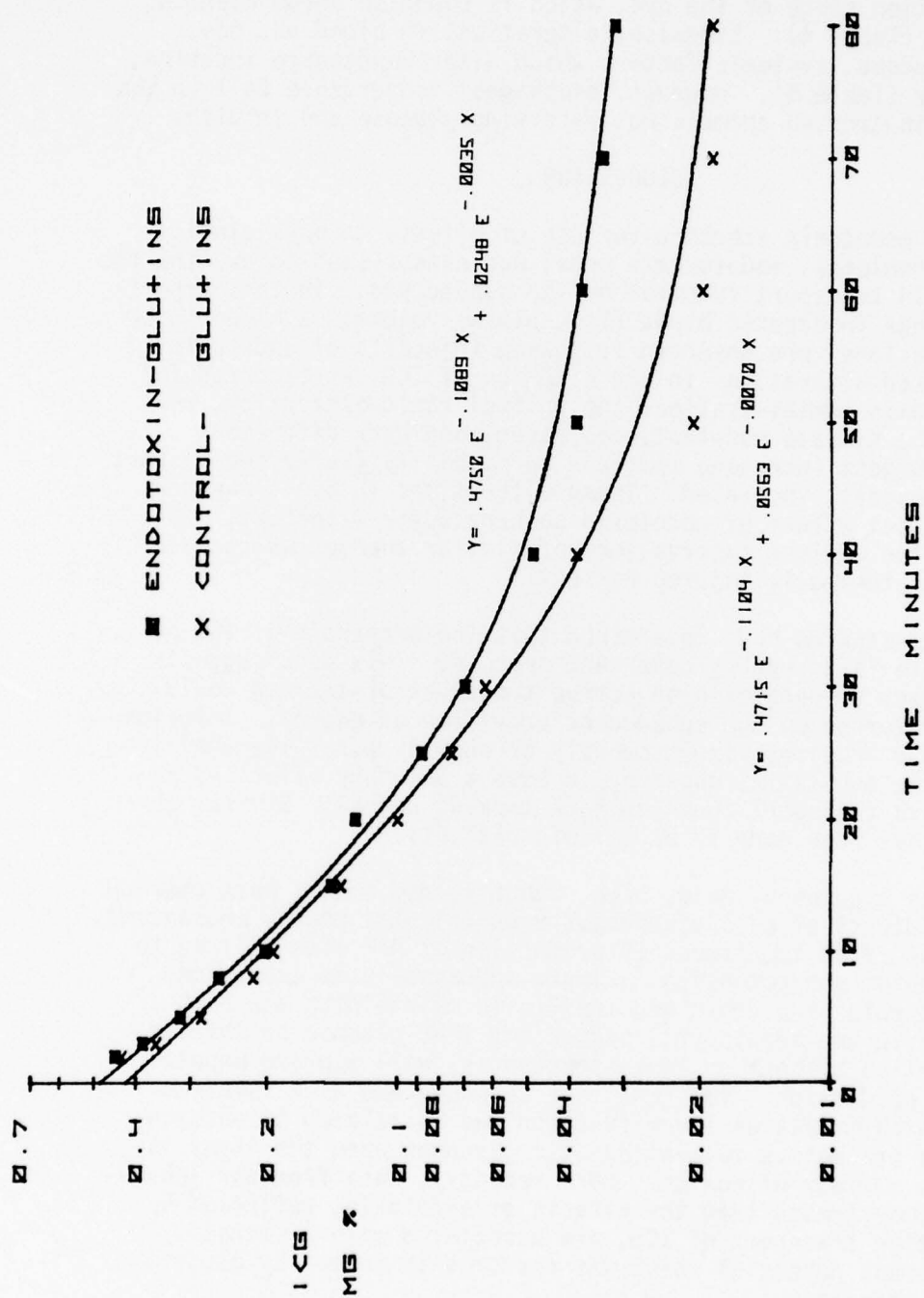


FIGURE 2

arterial or portal vein blood flow following administration of the nonlethal dose of endotoxin (Table 3). Similarly, no alteration in the distribution space of the dye, which is bound to serum albumin, was observed (Table 4). Likewise, alterations in blood pH,  $pO_2$ ,  $pCO_2$ , and glucose, systemic factors which alter hepatocyte function, did not occur (Table 5). However, esophageal temperature fell in the five endotoxin-treated animals not receiving glucose and insulin.

#### DISCUSSION

Because endotoxin exerts a variety of effects on physiologic function, a nonlethal endotoxemic model was established to examine the alterations in transport function of the hepatocyte. In this experiment, no change in hepatic blood flow, plasma volume, or blood pH or gas concentrations were observed following injection of endotoxin. However, marked alterations in the kinetics of ICG dye occurred following endotoxin administration; the initial rapid extraction, reflected by the  $K_1$  rate constant, decreased, and back diffusion, thought to suggest increased membrane permeability (reflected in part by the  $K_2$  constant) increased. These alterations in dye clearance suggest a direct effect of endotoxin on hepatocyte transport, substantiating the earlier observations of similar changes which occur in bacteremic thermally injured patients.

Previous studies have determined that the transport of ICG by the hepatocyte is an energy-dependent process. This data suggests that the effect of endotoxin on active transport of the dye could be readily reversed by the subsequent provision of energy. Infusion of glucose and insulin, simultaneously or shortly after the administration of the endotoxin, appeared to have a salutary effect of returning active transport function back towards normal. Similar observations have been made in bacteremic patients.

Previous studies by Mela, Baue, Schumer, and others have characterized the direct effects of endotoxin on cellular energy mechanisms, and have associated impairment in production of ATP with failure to transport sodium and potassium. Kimura and associates emphasized the specific role of glucose and insulin in maintaining the high energy store in the hepatocyte, suggesting that glucose or insulin, or a combination of both of these substances, will improve hepatocyte energy production. The impact of carbohydrate as a specific substance which maintains liver function may be related to observations of the protective role of hepatic glycogen when the liver is exposed to a variety of toxins. More recently, data from our laboratory have demonstrated that the effects of endotoxin, reflected by impaired active transport of ICG, are associated with a decrease in hepatic membrane potential which was restored to normal by glucose and insulin infusions.



MEAN HEPATIC BLOOD FLOW MEASUREMENTS (KHz)  
+ SE DURING VARIOUS EXPERIMENTAL CONDITIONS

	Control		Experiment		Observed Difference	
	Hep. Art.	P. Vein	Hep. Art.	P. Vein	Hep. Art.	P. Vein
Control n = 8	2.59 ± .41	1.23 ± .37	2.33 ± .33	1.18 ± .41	+0.26	+0.05
Endotoxin n = 16	2.99 ± .76	0.80 ± .17	3.05 ± .63	0.75 ± .14	-0.06	+0.05
Control + Gluc Ins n = 4	4.99 ± .16	0.92 ± .16	5.11 ± .13	0.89 ± .16	+0.12	-0.03
Endo + Gluc Ins n = 6	3.58 ± .58	0.54 ± 0.10	3.62 ± .37	0.48 ± .08	+0.04	-0.06

TABLE 3

COMPARISON OF PLASMA VOLUMES BY  
 $^{131}\text{I}$  Albumin and ICG

Plasma Volume cc/Kg Body weight $\pm$ SE	<u>Control (n=8)</u>		<u>Endotoxin (n=4)</u>	
	<u><math>^{131}\text{I}</math> Albumin</u>	<u>ICG</u>	<u><math>^{131}\text{I}</math> Albumin</u>	<u>ICG</u>
	47.0 $\pm$ 3.9	45.6 $\pm$ 2.5	49.6 $\pm$ 6.2	48.2 $\pm$ 5.2
Plasma Volumes (cc/Kg body wt. $\pm$ SE) Calculated From Initial Rate Constant of ICG Disappearance Under Various Experimental Conditions				
Control	38.7 $\pm$ 2.3	39.3 $\pm$ 1.6	47.9 $\pm$ 3.7	50.4 $\pm$ 4.3
Control			51.3 $\pm$ 6.2	50.9 $\pm$ 1.2
Control			49.3 $\pm$ 1.7	49.3 $\pm$ 1.4
Control				Endotoxin Gluc-Ins

TABLE 4

TABLE 5

SERUM STUDIES AND CORE TEMPERATURE UNDER VARIOUS EXPERIMENTAL CONDITIONS (MEAN $\pm$ SE)								
	Control	Control	Control	Endotoxin	Control	Control	Control	Endo- Gluc-Inc
	Control	Control	Control	Control	Gluc-Inc.	Control	Control	Gluc-Inc
GLUCOSE (mg%)	91 $\pm$ 4	91 $\pm$ 5	89 $\pm$ 3	88 $\pm$ 4	95 $\pm$ 2	142 $\pm$ 9	89 $\pm$ 3	113 $\pm$ 7
pH	7.290 $\pm$ .010	7.297 $\pm$ .012	7.206 $\pm$ .008	7.288 $\pm$ .011	7.292 $\pm$ .006	7.298 $\pm$ .009	7.293 $\pm$ .010	7.300 $\pm$ .007
pAO <sub>2</sub>	467 $\pm$ 6	472 $\pm$ 5	464 $\pm$ 6	445 $\pm$ 8	468 $\pm$ 5	471 $\pm$ 7	471 $\pm$ 7	447 $\pm$ 9
pACO <sub>2</sub>	40 $\pm$ 2	40 $\pm$ 4	39 $\pm$ 2	30 $\pm$ 3	41 $\pm$ 2	38 $\pm$ 2	43 $\pm$ 2	42 $\pm$ 3
Temp. (°F)	100.7 $\pm$ 0.3	100.1 $\pm$ 0.4	100.2 $\pm$ 0.2	98.9* $\pm$ 0.3	100.8 $\pm$ 0.2	100.4 $\pm$ 0.1	100.9 $\pm$ 0.3	100.5 $\pm$ 0.5

\*  $p < .01$  by paired  $t$  test

In summary, the observation of decreased hepatocyte active transport and increased membrane permeability which has been observed in man has been confirmed in an animal model. These alterations in ICG kinetics cannot be attributed to changes in blood flow, dye distribution space, or other systemic factors. These alterations in hepatic energetics can be returned toward normal by the simultaneous administration of glucose and insulin. In this model system, endotoxin is thought to have a direct effect on the hepatocyte transport, and may account for the progressive changes in hepatic function which are frequently observed in critically-ill infected patients.

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#### PRESENTATIONS

None

#### PUBLICATIONS

Heimbürger S, McDougal WS, Wilmore DW, Pruitt BA Jr: Hepatic and muscle membrane kinetics in the endotoxemic dog: a preliminary study for assessment of membrane function in the septic thermally injured soldier. In press, J Surg Res.

RESEARCH AND TECHNOLOGY WORK UNIT SUMMARY				1. AGENCY ACCESSION <sup>a</sup>	2. DATE OF SUMMARY <sup>a</sup>	REPORT CONTROL SYMBOL DD-DR&E(AR)656	
3. DATE PREV. SUMM <sup>a</sup>	4. KIND OF SUMMARY	5. SUMMARY SCTY <sup>a</sup>	6. WORK SECURITY <sup>a</sup>	7. REGRADING <sup>a</sup>	8a. DISB'S INSTR <sup>a</sup>	8b. SPECIFIC DATA - CONTRACTOR ACCESS	9. LEVEL OF SUM <sup>a</sup>
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10. NO./CODES <sup>a</sup>		PROGRAM ELEMENT		PROJECT NUMBER		TASK AREA NUMBER	
a. PRIMARY		61101A		3A161101A91C		00 089	
b. CONTRIBUTING							
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11. TITLE (Precede with Security Classification Code) <sup>a</sup> (U) Use of a Laminar Flow Isolator to Control Infection in Burned Troops (44)							
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NAME <sup>a</sup> US Army Institute of Surgical Research				NAME <sup>a</sup> US Army Institute of Surgical Research			
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23. (U) To assess the effectiveness of a laminar airflow isolator in infection control in burned soldiers.							
24. (U) Comparison of burn wound microbiology between laminar flow and conventionally treated patients will be made and related to septic complications and mortality in both groups.							

Available to contractors upon originator's approval.

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ANNUAL PROGRESS REPORT

PROJECT NO. 3A161101A91C-00, IN HOUSE LABORATORY INDEPENDENT RESEARCH  
REPORT TITLE: USE OF A LAMINAR FLOW ISOLATOR TO CONTROL INFECTION IN  
BURNED TROOPS

US ARMY INSTITUTE OF SURGICAL RESEARCH  
BROOKE ARMY MEDICAL CENTER  
FORT SAM HOUSTON, TEXAS 78234

1 October 1976 - 30 September 1977

investigators:

Richard C. Treat, MD, Major, MC  
Basil A. Pruitt, Jr., MD, Colonel, MC

Reports Control Symbol MEDDH-288(R1)

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ABSTRACT

PROJECT NO. 3A161101A91C-QQ, IN HOUSE LABORATORY INDEPENDENT RESEARCH

REPORT TITLE: USE OF A LAMINAR FLOW ISOLATOR TO CONTROL INJECTION IN  
BURNED TROOPS

US Army Institute of Surgical Research, Brooke Army Medical Center  
Fort Sam Houston, Texas 78234

Period covered in this report: 1 October 1976 - 30 September 1977

Investigators: Richard C. Treat, MD, Major, MC  
Basil A. Pruitt, Jr., MD, Colonel, MC

Reports Control Symbol MEDDH-288(R1)

Because of the high incidence of burn wound invasion causing lethal sepsis and studies showing cross contamination to be responsible for twice as many infections in burn patients as auto contamination, recent interest in patient isolation techniques has increased. Laminar air flow isolated units have shown a potential for reducing cross contamination in burn patients and therefore reducing the incidence of burn wound invasive infection. The Sci-Med Company of Minneapolis, Minnesota was therefore contacted to develop a laminar air flow unit to meet specific specifications. This unit was engineered, constructed and installed at the Institute of Surgical Research in 1977. Further modifications prior to patient use remain to be completed and it is expected that initial clinical trials will take place in 1978.

Burn injury  
Infection  
Laminar flow  
Humans



## USE OF A LAMINAR FLOW ISOLATOR TO CONTROL INFECTION IN BURNED TROOPS

It is well known that in recent years the development of infection has been the most common cause of death in burn patients. In reviewing our recent statistics, 62% of our mortality in 1976 was caused by sepsis. The vast majority of these cases resulted from invasive infection of burn wounds. Many attempts have been made to decrease the incidence of burn infection both by the use of various topical antibiotic agents and by early operative excision of the burn wound. Although improvement has been noted by utilizing these methods, certainly invasive burn wound infections still remain as a major cause of death in burn patients.

Studies have shown a significant difference in the number of infections caused by cross contamination and auto contamination. Cross contamination is responsible for almost twice as many infections in burn patients as auto contamination of the burn wound. Patient isolation techniques in a large open intensive care unit and separate isolation rooms for burn care have not resulted in low cross contamination rates in burn units.

Recent interest in laminar air flow isolator units has developed and preliminary studies have shown significant potential benefit with a reduction in cross contamination of burn wounds. A secondary advantage of these units is the controlled environment of increased ambient temperature and humidity which is conducive to the well being of the burn patient.

After reviewing the recent use of the units, it was felt to have shown sufficient potential to justify clinical investigation into the use of laminar air flow isolator units. Therefore the Sci-Med Company of Minneapolis, Minnesota was contracted to develop a laminar air flow unit to meet certain specifications. These specifications included the requirement that it be self-contained requiring only electrical power and tap water supply for operation; the size of the unit should be limited to the approximate size of an adult hospital bed, HEPA final filters (99.97% efficient at a particle size of 0.3 micron) should be utilized and return air duct work should be included to make the air circulation self-contained. Additionally the unit should be bounded on the sides by transparent curtains to allow complete visual contact with the patient and have slits along the sides for the entire length of the unit to permit easy access to the patient. Heat and humidity environmental control should be an integral part of the unit. High and low air velocity of  $40 \pm 10$  and  $25 \pm 10$  feet per minute during operations should be available. The maximum internal noise level should be N.C. 50 db.

The unit was delivered and installed in August 1977. Permanent electrical hook-up and steam line hook-up for humidity control remain to be completed. Modifications in the side curtains are currently being undertaken by the Sci-Med Company. It is expected that the unit

will be completed and functional in the relatively near future.

Several studies are planned for patients in the laminar air flow isolation unit. First it must be determined that adult patients can be properly cared for in this environment which somewhat decreases nursing access to these patients. With the high level of inhalation injuries and mechanical ventilatory support utilized by patients in the Institute of Surgical Research, newer care techniques need to be worked out for patients in the isolator units. Thereafter studies of auto contamination and cross contamination of patients in our burn unit will be completed and following these different therapeutic maneuvers such as early massive excision in adult burns will be attempted with careful monitoring of the bacteriological results. Special studies of potential psychological effects of such an isolation unit in long term care of critically ill patients will receive attention.

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RESEARCH AND TECHNOLOGY WORK UNIT SUMMARY					1. AGENCY ACCESSION*	2. DATE OF SUMMARY*	REPORT CONTROL SYMBOL DD-DR&E(AR)656	
3. DATE PREV. SUMMARY	4. KIND OF SUMMARY	5. SUMMARY SCTY*	6. WORK SECURITY*	7. REGRADING*	8A. DISSEM INSTR*	8B. SPECIFIC DATA- CONTRACTOR ACCESS	9. LEVEL OF SUM	
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A. PRIMARY	61101A	3A161101A91C		00	084			
B. CONTRIBUTING								
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11. TITLE (Precede with Security Classification Code)* (U) Echocardiographic Evaluation of Left Ventricular Performance in The Severely Burned Military Population (44)								
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003500 Clinical Medicine								
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NAME* US Army Institute of Surgical Research				NAME* US Army Institute of Surgical Research				
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(U) Resuscitation; (U) Burned soldiers; (U) Left ventricular function								
23. TECHNICAL OBJECTIVE, 24. APPROACH, 25. PROGRESS (Furnish individual paragraphs identified by number. Precede text of each with Security Classification Code.)								
23. (U) The military relevancy is to evaluate left ventricular function in thermally injured soldiers, especially in the postburn shock phase. To evaluate the hypothesis that myocardial depression is a direct consequence of severe thermal injury.								
24. (U) Serial left ventricular performance profiles will be derived echocardiographically and correlated to the clinical state of the patient.								
25. (U) 76 10 - 77 09 Serial echocardiographic (ECHO) evaluation of left ventricular function has been performed in 83 thermally injured patients. This represents 62% of all patients admitted with a total body surface burn of greater than 30%. Seven hundred forty-nine echograms have been performed (62 per month or 2.1 per day). Conclusions are as follows: (1) ECHO LV function during postburn resuscitation (in = 116 serial studies) reveals no evidence of myocardial depression secondary to acute thermal injury. (2) ECHO LV volume during inhalation injury (n = 100 studies) reveals marked fluctuations during inspiratory-expiratory phases. (3) ECHO LV function during the utilization of PEEP for the treatment of pulmonary complications does not reveal a decrease in myocardial contractility (n = 256 studies). (4) ECHO is not a sensitive diagnostic method to evaluate right-sided valvular integrity in suspected endocarditis (n = 150 studies).								

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ANNUAL PROGRESS REPORT

PROJECT NO. 3A161101A91C-00, IN-HOUSE LABORATORY INDEPENDENT RESEARCH

REPORT TITLE: ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR PERFORMANCE IN THE SEVERELY BURNED MILITARY POPULATION

US ARMY INSTITUTE OF SURGICAL RESEARCH  
BROOKE ARMY MEDICAL CENTER  
FORT SAM HOUSTON, TEXAS 78234

1 October 1976 - 30 September 1977

Investigators:

James F. Dorethy, M.D., Major, MC

Reports Control Symbol MEDDH-288(R1)

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# ABSTRACT

PROJECT NO. 3A161101A91C-00, IN-HOUSE LABORATORY INDEPENDENT RESEARCH

REPORT TITLE: ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR PERFORMANCE IN THE SEVERELY BURNED MILITARY POPULATION

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Period covered in this report: 1 October 1976 - 30 September 1977

Investigators: James F. Dorethy, M.D., Major, MC

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Echocardiography (ECHO) was utilized to monitor left ventricular (LV) performance after acute thermal injury and its complications. Serial ECHO was performed in 90 thermally injured patients. Previously reported myocardial depression could not be recognized in (1) early postburn "shock," (2) postburn resuscitation, (3) acute respiratory failure treated with continuous positive pressure ventilation, and (4) hyperdynamic phase of septic "shock." Myocardial depression was noted during late phases of bacteremic shock, especially with myocardial abscesses. ECHO was not found to be a sensitive diagnostic method to evaluate right-sided valvular vegetation in suspected endocarditis. Other cardiovascular entities studied were (1) pericardial effusion and impending tamponade, (2) systolic anterior motion of mitral valve during hypovolemia, (3) hypertrophic cardiomyopathy, and (4) respiratory swings in LV volume after inhalation injury.

Postburn shock  
Echocardiography  
Resuscitation  
Left ventricular function  
Burned soldiers

## ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR PERFORMANCE IN THE SEVERELY BURNED MILITARY POPULATION

Monitoring the cardiovascular response to acute thermal injury, postburn resuscitation, and subsequent complications is difficult and often requires invasive techniques. A promising noninvasive technique to evaluate left ventricular (LV) performance in these situations is echocardiography (ECHO). ECHO LV ejection indices and volumes compare favorably with those obtained by angiographic contrast studies (1-4). It has also been of diagnostic significance in pericardial effusion and tamponade (5-6), bacterial endocarditis (7), hypertrophic obstructive cardiomyopathy (8-9), rheumatic valvular disease (10), and some aspects of ischemic heart disease (11).

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Serial measurements of acute LV dimensional alterations during heart rate change (12), afterload alteration (12), intravascular volume change (13), and positive or negative inotropic intervention (14-15) have been reported. ECHO studies on normal populations have established quantitative and qualitative guidelines (16-17). Autopsy comparison of LV and septal wall size reveals close correlation (18). The limitations and resolution capabilities of single mode ECHO scanning are well known (19-21).

Potential usages of ECHO in a burn intensive care center are:  
(1) evaluation of LV performance during early postburn resuscitation,  
(2) diagnosis of pre-existing cardiovascular (CV) disease, (3) evaluation of cardiac and pulmonary components in respiratory failure,

- 
12. Hirshleifer J, Crawford M, O'Rourke RA, Karliner JS: Influence of acute alterations in heart rate and systemic arterial pressure on echocardiographic measures of left ventricular performance in normal human subjects. *Circulation* 52:835-841, 1975.
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(4) evaluation of LV performance during sepsis and subsequent therapy, and (5) evaluation of the appearance of valvular integrity in suspected endocarditis.

This study evaluated serial ECHO LV performance during postburn hospitalization. This method was compared with other clinical and invasive monitoring techniques. Several ECHO categories of clinical interest were established: (1) early postburn volume resuscitation, (2) cardiopulmonary hemodynamics with inhalation injury, (3) acute respiratory failure, (4) severe bacteremia and septic shock, (5) suspected acute bacterial endocarditis, (6) LV inotropic therapy, and (7) miscellaneous CV complications. This report summarizes the findings to date in each of these categories.

## METHODS AND MATERIALS

### Technique

All studies were performed with a specially designed mobile Honeywell ECHO/hemodynamic unit interfaced with a Honeywell 1858 Visicorder and Hewlett-Packard 1317A display scope. M-mode echograms were obtained with a commercially available Echoline 20A ultrasonoscope. Transducers included 3.5 and 2.25 MHz sizes focused at 5, 7.5 and 10 cm. Transducers of higher frequency and variable focal distance were used whenever possible to facilitate the recording of detailed ECHO anatomy.

All studies were performed with minimal interruption of routine and emergency care. Patients were studied initially, and then serially as their clinical course dictated. All were studied supine, semi-erect, or in a semi-left lateral position. The patient position, transducer angulation and standard interspace were carefully noted. Standard interspace was defined as the transducer being perpendicular to the chest wall with visualization of the anterior mitral leaflet (22). The external relationship of the transducer to the heart was duplicated as closely as possible in serial studies. Only qualitative ECHO findings were used in those patients without adequate ECHO "windows" required for an M-mode sector scan. No attempt was made to establish the efficacy of the technique in every patient. Only those with adequate echograms as defined above were included in serial follow-up. However, those patients suspected of acute bacterial endocarditis (ABE) were excluded from this requirement. No actual dimensional measurements were attempted in these cases. All studies were performed during inspiration and expiration.

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22. Popp RL, Filly K, Brown OR, Harrison DC: Effect of transducer placement on echocardiographic measurements of left ventricular dimensions. *Am J Cardiol* 35:537-540, 1975.



The ECHO measurements used to evaluate LV performance are listed in Table 1. These were obtained by analyzing 5 to 10 consecutive beats after establishing the optimum area by an M-mode sector scan using variable gain control. The septum and posterior wall were traced by a hand-held digitizer and relayed to a programmable 9830 Hewlett-Packard desk computer. This was then transferred to graph form displaying both end systolic and end diastolic values for each beat. Derived volumes were calculated from the LV dimensions by using Teichholz's empirical formula (4).

Table 1. Echocardiographic Measurements of Left Ventricular Function

- 
1. LV end diastolic dimension (EDD, mm)
  2. LV end systolic dimension (ESD, mm)
  3. LV end diastolic volume (EDV, cc)
  4. LV end systolic volume (ESV, cc)
  5. Stroke volume ( $SV = EDV - ESV$ , cc/bt)
  6. Ejection fraction ( $EF = EDV/SV$ , %)
  7. Mean rate of internal fiber shortening ( $V_{cf}$ , circ/sec)
  8. ECHO-cardiac output ( $HR \times SV = CO$ , L/min)
- 

An ECHO M-mode sector scan is shown in Figure 1. The area digitized in the LV cavity is depicted in Figure 2. Figures 3 and 4 are representative volume and dimension curves. Inspiratory and expiratory measurements were averaged over 3 to 5 respiratory cycles when marked differences occurred. Only expiratory measurements were used when dense anterior inspiratory echoes were prominent.

All values were compared to a normal ECHO population. These were patients who had normal right and left heart catheterizations (courtesy of Brooke Army Medical Center, Cardiac Catheterization Laboratory, LTC Joseph P. Murgo, M.D., Chief). These normal values and their corresponding angiographic measurements are listed in Table 2. Statistical analysis was performed using a Student t-test for unpaired data.

#### Patients

A total of 90 patients were studied. Seven had total body surface burns (TBSB) of less than 30%. The other 83 represent 62% of the total admissions with over 30% TBSB during this study period. One hundred forty-one patient ECHO studies were performed. Patients were evaluated regardless of age, sex, degree of anterior thorax involvement or clinical condition on admission. Some patients were

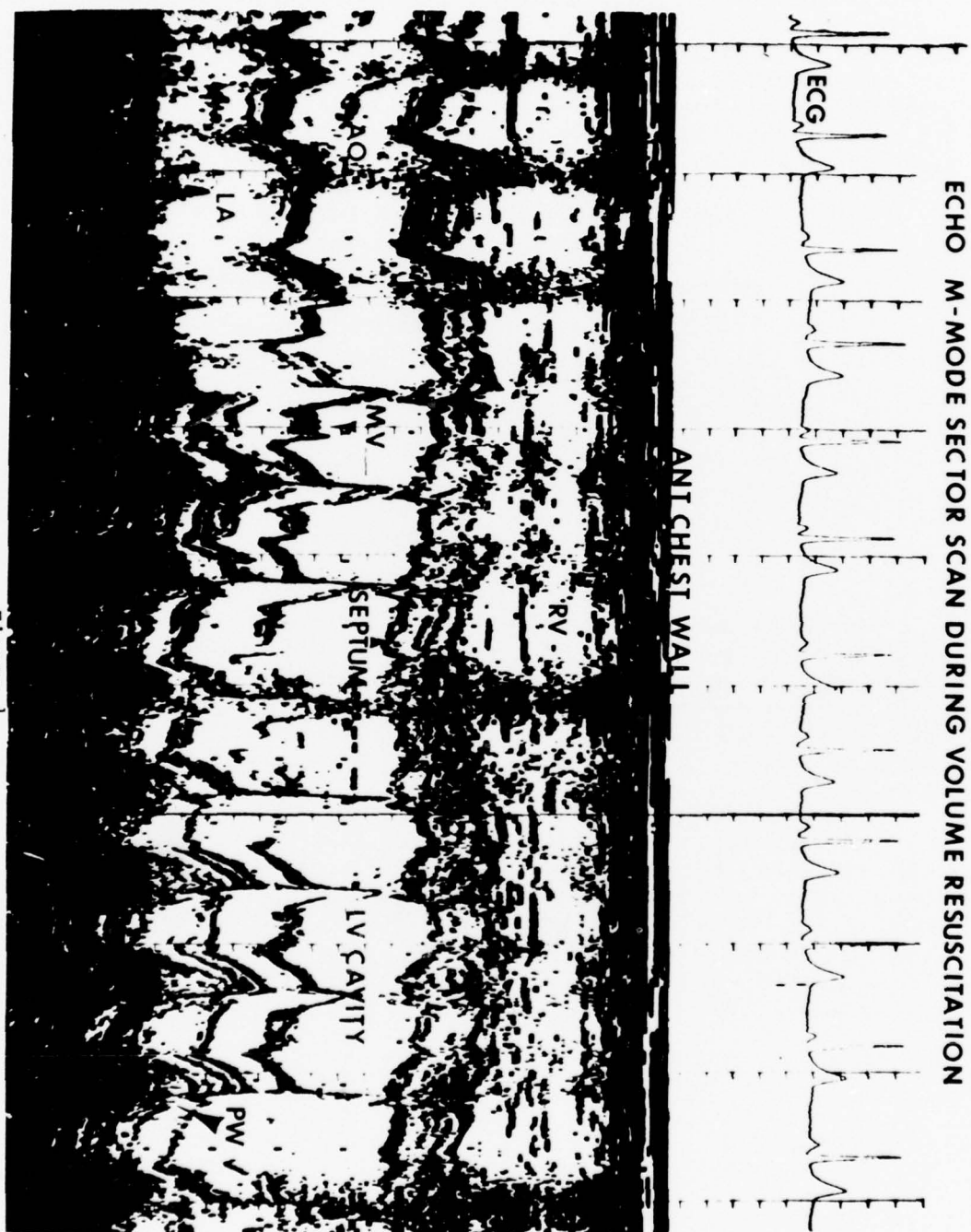


Figure 1

# ECHO LV INTERNAL DIMENSIONS

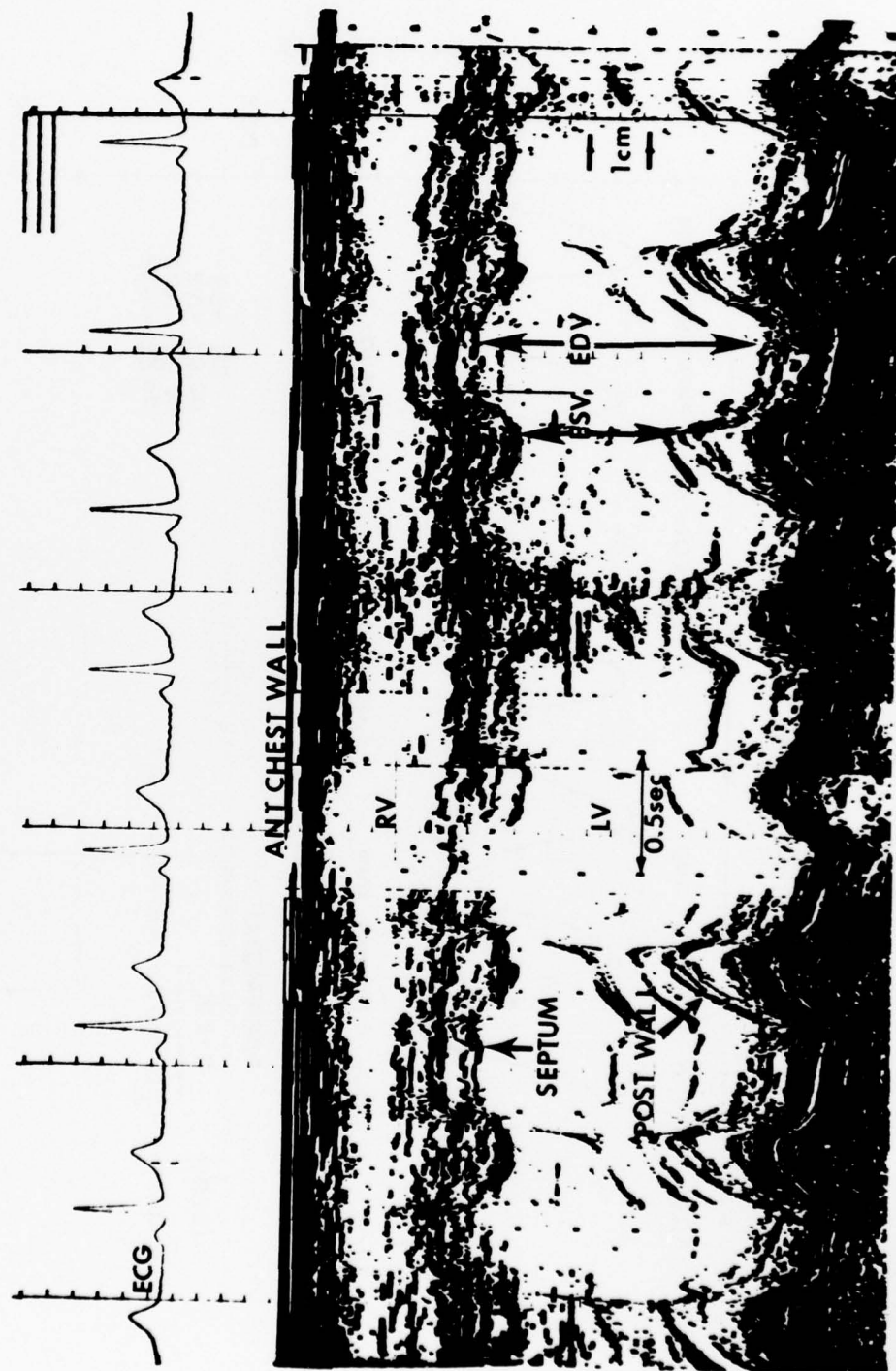


Figure 2

# ECHOCARDIOGRAPHIC LEFT VENTRICULAR VOLUME

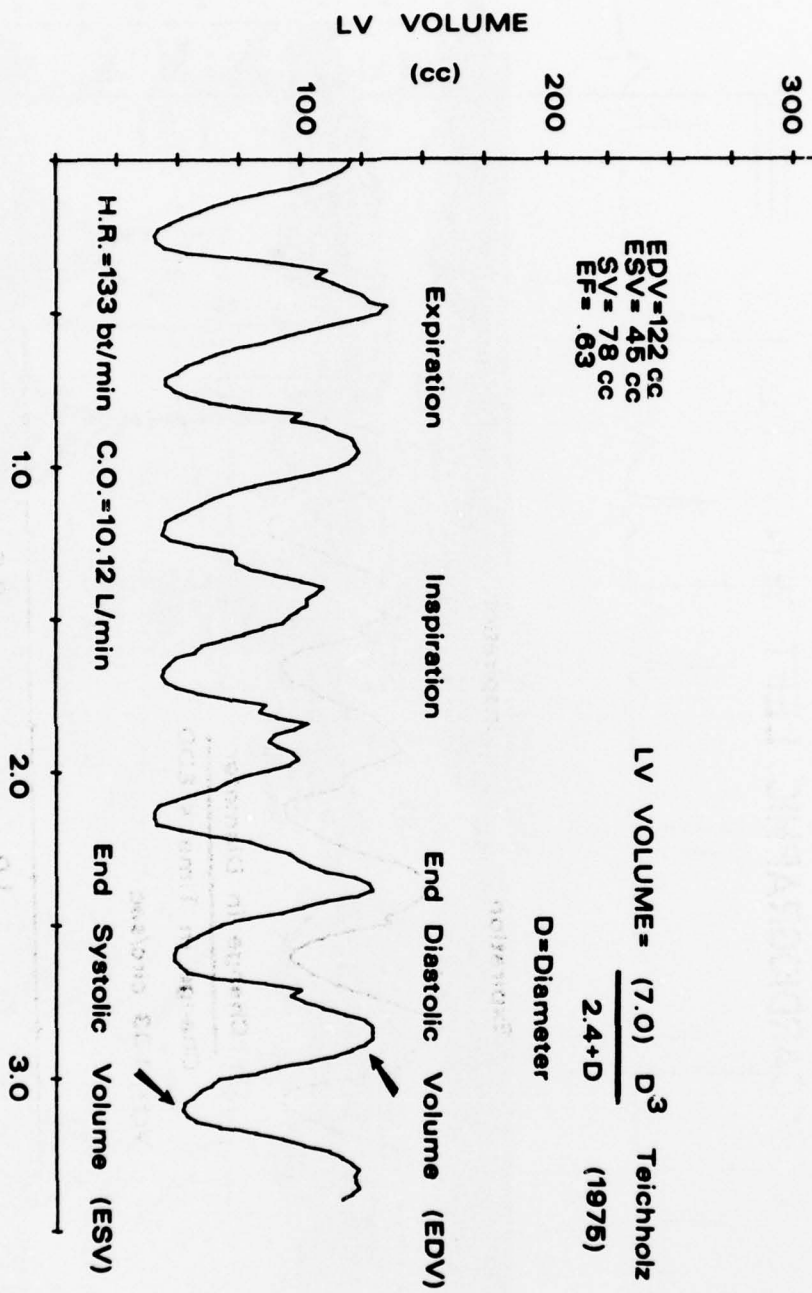


Figure 3



# ECHOCARDIOGRAPHIC LEFT VENTRICULAR DIMENSIONS

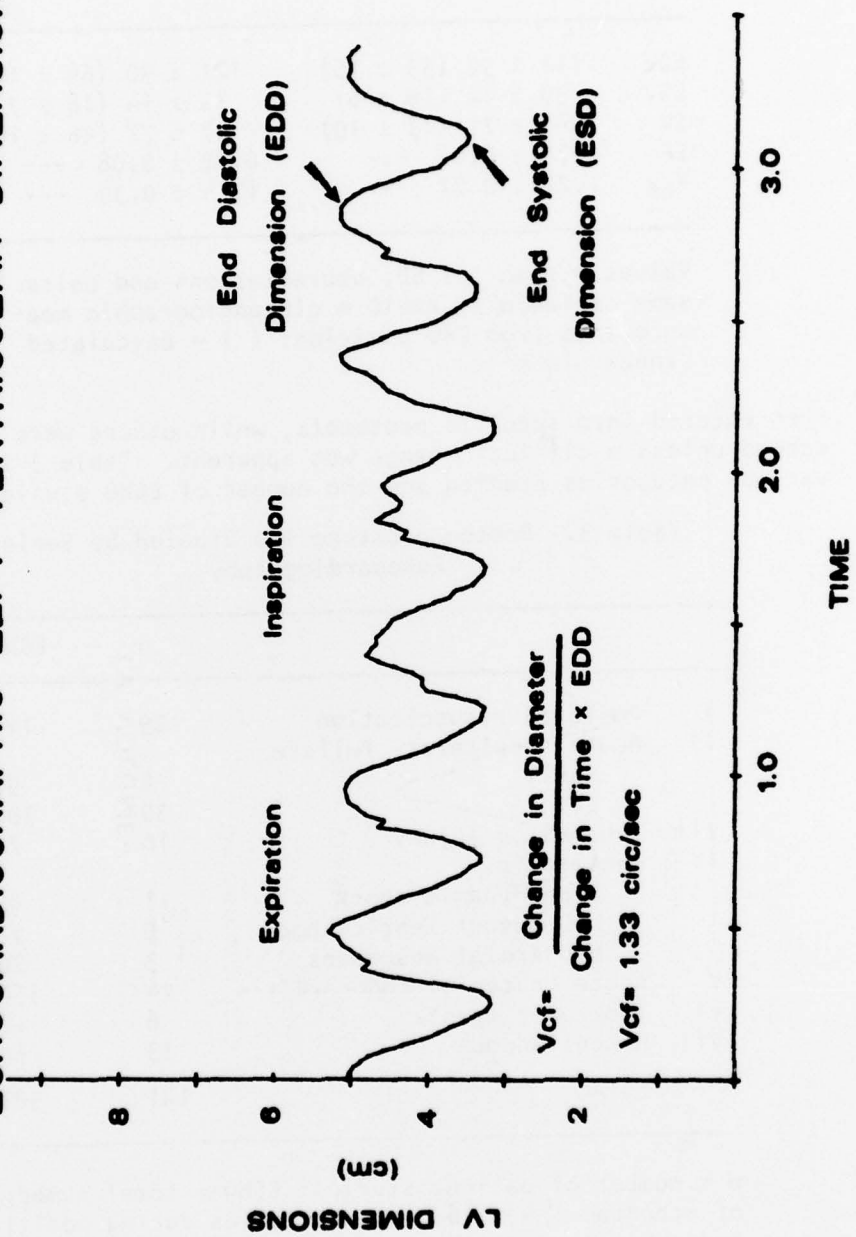


Figure 4

Table 2. Normal ECHO Left Ventricular Indices Compared to Angiographic Indices

n = 25    Age = $38 \pm 7$ BSA = $1.86 \pm 0.19$					
ECHO			ANGIO		
EDV	$111 \pm 32$	( $59 \pm 15$ )	$121 \pm 30$	( $64 \pm 14$ )	
ESV	$30 \pm 12$	( $16 \pm 6$ )	$34 \pm 14$	( $18 \pm 7$ )	
SV	$81 \pm 21$	( $43 \pm 10$ )	$87 \pm 22$	( $46 \pm 10$ )	
EF	$0.74 \pm 0.06$	---	$0.72 \pm 0.08$	---	
V <sub>cf</sub>	$1.22 \pm 0.22$	---	$1.44 \pm 0.34$	---	

Values = mean  $\pm$  1 SD; abbreviations and units same as Table 1; ANGIO = cineangiographic measurements from LAO position; ( ) = calculated "index" in m<sup>2</sup>

then entered into specific protocols, while others were not re-echoed unless a clinical change was apparent. Table 3 lists the various categories studied and the number of ECHO studies in each.

Table 3. Postburn Categories Studied by Serial Echocardiography

		n	ECHO
I	Postburn resuscitation	29	116
II	Acute respiratory failure		
	Early	4	50
	Late	30*	308
III	Inhalation injury	16	72
IV	Bacteremia		
	Hyperdynamic shock	11	45
	Low output septic shock	5	20
	Myocardial abscesses	3	20
V	Acute bacterial endocarditis	24	150
VI	Inotropic agents	6	60
VII	Miscellaneous	13	50
TOTAL		141	901

n = number of patient studies; ECHO = total number of echograms; \* = 16 patient studies during positive end expiratory pressure therapy

## RESULTS

### Postburn LV Function

Twenty-nine patients were studied in the immediate postburn period (0-72 hr). One hundred sixteen serial ECHO's were performed. Table 4 lists the patient characteristics and clinical course.

Table 4. Patient Characteristics Postburn

No. patients	29
Age	$34 \pm 14$
TBSB (%)	$69 \pm 21$
Time studied postburn (hrs)	$10.6 \pm 4.0$
Postburn to death (days)	$6.6 \pm 4.1$
Mortality	18/29 (65%)
Autopsy	13/18 (72%)

The patients were young ( $34 \pm 14$  years), with extensive TBSB ( $69 \pm 21$  percent). Several distinct ECHO-hemodynamic profiles were recognized (Table 5). In the initial time period (0-12 hr postburn), LV volumes were within normal range, LV ejection dynamics were hypercontractile, and cardiac outputs were low. In the middle time period (12-24 hr), ejection dynamics continued to be high. Cardiac outputs were supra-normal in the 24-48 hr period with excellent LV performance. No evidence of depressed myocardial function occurred within 72 hours postburn in any patient, regardless of resuscitation regimen.

Table 5. Left Ventricular Performance during Postburn Resuscitation

	0-12 Hr	12-24 Hr	24-48 Hr
*ECHO CI	$3.08 \pm 0.32$	$3.71 \pm 0.26$	$4.23 \pm 0.27$
EDVI	$42 \pm 5$	$46 \pm 4$	$52 \pm 4$
SI	$33 \pm 4$	$34 \pm 2$	$38 \pm 3$
EF	$0.79 \pm 0.02$	$0.75 \pm 0.02$	$0.75 \pm 0.02$
V <sub>cf</sub>	$1.66 \pm 0.12$	$1.77 \pm 0.10$	$1.66 \pm 0.16$

Values = mean  $\pm$  1 SEM; \* normal ECHO CO =  $3.40 \pm 0.04$  L/min/m<sup>2</sup>; I = index in m<sup>2</sup>; abbreviations and units same as Table 1

Four patients with extensive burns died within 72 hours after injury. Their LV ejection dynamics remained normal to hypercontractile until their terminal event (Table 6). All died from resistant low CO, severe inhalation injury, and terminal arrhythmias.

Table 6. Patients with a Rapidly Fatal Clinical Course Postburn

	Patients				Total
	A	B	C	D	
Age	58	45	45	23	43±15
TBSB (%)	61	82	83	93	80±13
RL (L/24 hr)	20	29.5	26	24.8	25.1±3.9
EF	0.67±0.06	0.82±0.04	0.81±0.03	0.87±0.08	0.79±0.09
V <sub>cf</sub>	1.85±0.37	2.03±0.17	1.57±0.18	2.14±0.11	1.80±0.25
ECHO-CO	2.50±0.14	1.90±0.53	3.30±0.14	2.90±0.31	2.65±0.60
pH	7.27±0.07	---	7.34±0.19	7.03±0.01	7.21±0.16

Values = mean ± 1 SD; RL = Ringer's lactate; pH = arterial blood pH; abbreviations and units same as Table 1

All received massive amounts of crystalloid fluid resuscitation and experienced severe respiratory difficulties. The inability to re-establish an adequate perfusion output was not related to myocardial dysfunction.

#### Acute Respiratory Failure

The cardiovascular function of 34 patients with acute respiratory failure (ARF) was evaluated by ECHO. Table 7 lists the apparent etiology of their respiratory failure.

Table 7. Etiology of Acute Respiratory Failure as a Complication of Acute Thermal Injury

Etiology	n
Sepsis	24
Volume overload	4
Inhalation injury	6

n = number of patients

On the basis of their LV performance, this group could be divided into three subgroups (Table 8). Group I had no abnormal ECHO findings associated with their pulmonary insufficiency and represented a pure adult respiratory distress syndrome (ARDS). Group II exhibited an element of abnormal LV function and apparently had a dual reason for their ARF. Two patients (Group III) had markedly



abnormal ECHO LV function, and their respiratory difficulties were secondary to pulmonary edema.

Table 8. Left Ventricular Function in Patients with Pulmonary Insufficiency

Group	EDV	EF	V <sub>cf</sub>
I	108 ± 23	0.68 ± 0.05	1.66 ± 0.44
II	165 ± 4*	0.60 ± 0.02*	1.32 ± 0.16
III	181 ± 18*	0.38 ± 0.05*	0.66 ± 0.15*

Values = mean ± 1 SD; \* p = < 0.01 compared to Group I; abbreviations and units same as Table 1

Acute respiratory failure treated with continuous positive pressure ventilation was also studied in 19 patients. Those studies form the basis of another report.

#### Inhalation Injury

One patient with marked inhalation injury and minor TBSB (10%) was studied serially. The results are summarized in Table 9.

Table 9. Phasic Respiratory Changes in Left Ventricular Volumes after Inhalation Injury

18-year-old, 10% TBSB, severe inhalation injury						
Clinical Status		EDV	SV	EF	V <sub>cf</sub>	Paradoxical Pulse (mmHg)
Admission (PaO <sub>2</sub> = 58 torr)	Exp	20	16	0.83	2.40	30
	Insp	19	17	0.90	3.75	
Volume repletion (PaO <sub>2</sub> = 55 torr)	Exp	128	93	0.73	1.74	28
	Insp	105	80	0.77	1.94	
Recovery (PaO <sub>2</sub> = 82 torr)	Exp	112	88	0.79	1.49	8
	Insp	102	80	0.78	1.54	

Exp = expiration; Insp = inspiration; abbreviations and units same as Table 1; PaO<sub>2</sub> = arterial blood gases

Early LV volume measurements revealed marked volume depletion. He had a significant pulsus paradoxus after volume repletion, associated with ECHO fluctuations in inspiratory and expiratory stroke volume (Figure 5). Qualitatively, the ECHO is similar to those found in cases of cardiac tamponade, i.e., right ventricular compression, abnormal septal motion, and decreased mitral valve E-F slope. However, no evidence of pericardial effusion was present. After all objective evidence of the inhalation injury disappeared, the pulsus paradoxus, ECHO signs of "tamponade," and marked phasic respiratory stroke volume changes were no longer present. Other patients with evidence of inhalation injury had similar ECHO respiratory "swings," and pulsus paradoxus.

### Severe Bacteremia

Nineteen patients were evaluated during various stages of severe bacteremia. The ECHO-LV findings are listed in Table 10 on six of these. Their LV performances were variable, as was their response to inotropic agents. Three distinct subgroups were recognized: (1) hyperdynamic septic shock, (2) low output septic shock, and (3) myocardial abscesses. The first group exhibited high CO, but they were unable to maintain an adequate arterial blood pressure. The low output septic shock group had abnormally low CO, even on pressors, and steadily decreasing LV function. Those patients with myocardial abscesses revealed hyperdynamic LV performance which abruptly became abnormal. This change heralded a rapidly declining clinical course. No therapeutic intervention was successful in reversing this trend.

Table 10. Left Ventricular Performance in Severe Septicemia

n	Clinical Onset of Sepsis		During Treatment		Post-treatment	
	EF	V <sub>cf</sub>	EF	V <sub>cf</sub>	EF	V <sub>cf</sub>
2	0.69	1.74	0.67	1.75*	0.70	1.90
1	0.71	1.48	0.67	1.41*	0.55	1.30*
1	0.58	1.26	0.63	1.48*	0.73	2.01
1	0.58	1.18	0.74	2.10*	0.41	1.03*
1	0.61	1.68	0.57	1.14*	0.61	1.26*

\* Patients on dopamine; n = number of patients; abbreviations and units same as Table 1

ECHOGRAM ON PATIENT WITH SEVERE INHALATION INJURY AND  
PULSUS PARADOXUS

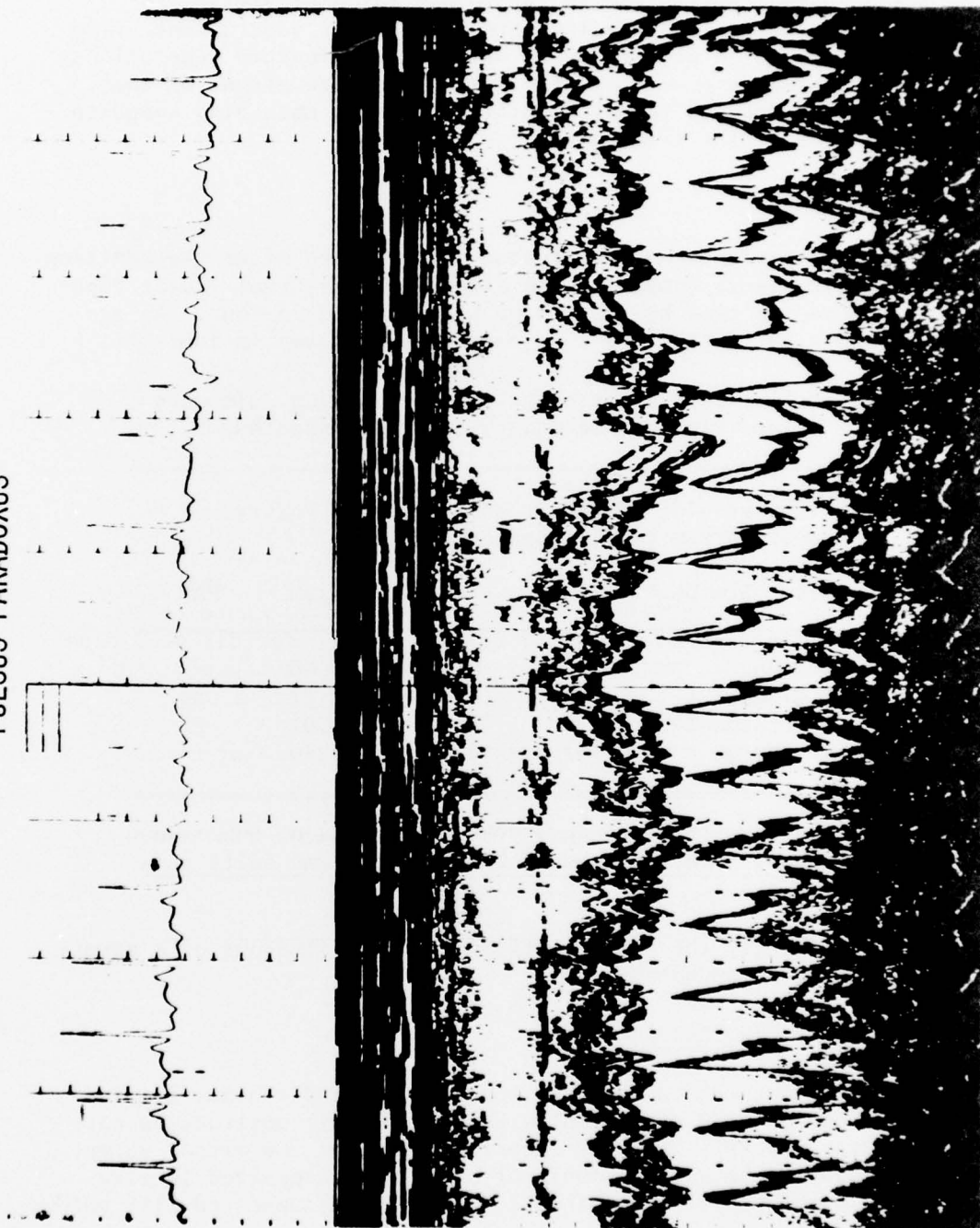


Figure 5

### Acute Bacterial Endocarditis

Twenty-four patients with staphylococcal bacteremia were serially evaluated for valvular integrity and/or vegetations. Two patients were noted at autopsy to have large tricuspid vegetations. Their ECHO studies pre-mortem failed to recognize either of them. This was secondary to technical difficulties in obtaining adequate visualization of the tricuspid valve.

### Inotropic Agents

Several patients were evaluated prior to and after the addition of inotropic agents (dopamine and digoxin). Left ventricular function improved in two, but no change was recorded in four. An example from a patient with a cardiomyopathy is given in Table 11.

Table 11. Left Ventricular Function during Pulmonary Insufficiency Secondary to Cardiomyopathy

17-year-old; 45% TBSB; no inhalation injury; post-partum cardiomyopathy				
Clinical Status	EDV	EF	V <sub>cf</sub>	PAW
Admission	143	0.67	1.58	--
ARDS diagnosis	177	0.33	0.72	25
Post-treatment*	116	0.57	1.01	22
At discharge	147	0.40	0.70	--

\* Treated with diuretics, CPPV, and digoxin; PAW = mean pulmonary arterial wedge; abbreviations and units same as Table 1

At discharge, the patient still exhibited findings of a severe compensated cardiomyopathy.

### Miscellaneous ECHO Findings

One patient with a markedly abnormal ECG and minimal clinical findings had an ECHO consistent with hypertrophic obstructive cardiomyopathy (HOCM). Systolic anterior motion of the mitral valve, once thought to be pathognomonic of HOCM, was recognized in five patients with hypovolemia. This ECHO finding disappeared with volume expansion.



One patient with a large staphylococcal pericardial effusion revealed all the classic ECHO signs of tamponade. Pericardiocentesis did not alleviate these ECHO findings, and the patient rapidly succumbed to the infection.

Lack of ECHO findings in patients with a history of rheumatic fever was helpful in ruling out valvular involvement. Linear ECHO scanning failed to demonstrate abnormal wall motion in several patients with a history of ASHD. These findings were correlated to autopsy findings where possible.

#### DISCUSSION

This study establishes ECHO as a useful technique to monitor serially cardiovascular function in the Critical Care Unit (CCU). It was utilized in every clinical state that arose as a complication of acute thermal injury. Under the right conditions, it replaced the necessity of invasive monitoring. ECHO also represented a more accurate anatomical and functional picture of LV performance. Therapy, i.e., fluid resuscitation, inotropic agents, and CPPV, was easily monitored and its effects on LV performance evaluated. Ineffectual or harmful therapy could be modified or discontinued as needed. Difficult cardiovascular diagnostic problems in the CCU, i.e., ARDS, pericardial effusion, myocardial abscesses, hypovolemia, or acute cardiomyopathies were more easily recognized and prompt treatment initiated. The ECHO studies also established new concepts and understanding of cardiopulmonary interaction. It also discredited several misconceptions about LV function following thermal injury, during septicemia and during the decreased CO with CPPV.

Several clinical situations were noted to exhibit ECHO findings that have been established in unrelated disorders, thereby providing additional guidelines to the differential diagnosis of pulsus paradoxus, cardiac tamponade, and systolic anterior motion of the mitral valve.

The absence or presence of preburn cardiovascular abnormalities was easier to define. The only situation in which ECHO did not prove useful was in prospectively detecting valvular vegetations in acute bacterial endocarditis. This was a technical limitation of the method itself, and further equipment refinement needs to be evaluated.

It is concluded that ECHO is an excellent adjunct to modern monitoring techniques of cardiovascular function in the CCU. Correlation of this to other sophisticated hemodynamic equipment requires continued comparison. Further studies have been initiated

on the ECHO evaluation of septic shock, LV performance during large shifts in intrathoracic pressure, and LV function with varying resuscitation regimens.

#### PRESENTATIONS

Dorethy JF: Acute bacterial endocarditis as a silent source of sepsis. American College of Cardiology, 25th Annual Scientific Session, New Orleans, Louisiana, 14 February 1977.

Dorethy JF: The application of serial echocardiography in severely burned patients. Society of Critical Care Medicine, 6th Annual Scientific and Education Symposium, New York, New York, 13 March 1977.

Dorethy JF: Echocardiography in a critical care unit: Left ventricular ejection dynamics following severe thermal injury and its complications. Association of Army Cardiology, 6th Annual Session, El Paso, Texas, 13 April 1977.

Dorethy JF: Burn resuscitation monitoring by echocardiography. US Army Institute of Surgical Research Thirtieth Anniversary Symposium, San Antonio, Texas, 24 June 1977.

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